



2010

New Cyclophanes as Supramolecular Scaffolds: The Synthesis of Tribenzo-1,4,7-Triazacyclononatriene.

Andria M. Panagopoulos
Loyola University Chicago

Recommended Citation

Panagopoulos, Andria M., "New Cyclophanes as Supramolecular Scaffolds: The Synthesis of Tribenzo-1,4,7-Triazacyclononatriene." (2010). *Dissertations*. Paper 88.
http://ecommons.luc.edu/luc_diss/88

This Dissertation is brought to you for free and open access by the Theses and Dissertations at Loyola eCommons. It has been accepted for inclusion in Dissertations by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.



This work is licensed under a [Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License](https://creativecommons.org/licenses/by-nc-nd/3.0/).
Copyright © 2010 Andria M. Panagopoulos

LOYOLA UNIVERSITY CHICAGO

NEW CYCLOPHANES AS SUPRAMOLECULAR SCAFFOLDS:
THE SYNTHESIS OF TRIBENZO-1,4,7-TRIAZACYCLONONATRIENE

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

PROGRAM IN CHEMISTRY

BY
ANDRIA M. PANAGOPOULOS

CHICAGO, ILLINOIS

AUGUST 2010

Copyright by Andria M. Panagopoulos, 2010
All rights reserved

ACKNOWLEDGEMENTS

I would like to sincerely thank my advisor, Daniel P. Becker, Ph.D. for all his support and guidance throughout the years. I have learned so much from you, not only about chemistry, but about myself and for that I thank you.

I would also like to thank my friends and family. You guys have stood by my side, encouraged me and supported me. I could not have completed this without your love and support. Thank you.

For Papa

I wish you were here.

For My Family,

Thank you.

Insanity – Doing the same thing over and over again and expecting different results.

-Albert Einstein

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	iii
LIST OF SCHEMES	vi
LIST OF FIGURES	viii
LIST OF TABLES	ix
LIST OF ABBREVIATIONS	x
ABSTRACT	xiv
CHAPTER 1 - AN INTRODUCTION TO SUPRAMOLECULAR CHEMISTRY, CTV AND N3-CTV	1
Supramolecular Chemistry	1
Cyclophanes	2
Cyclotrimeratrylene (CTV)	4
1,4,7-Triazacyclononane (TACN)	7
Tribenzo-1,4,7-Triazacyclononatriene (N3-CTV)	9
CHAPTER 2 – ATTEMPTED CONVERGENT SYNTHESIS OF N3-CTV	12
Convergent Trimerization	15
[2x1] Dihalide Convergent Synthesis	22
[2x1] Diamino Convergent Synthesis	25
Templated Convergent Synthesis	29
CHAPTER 3 – LINEAR SYNTHETIC STRATEGY AND THE FORMATION OF THE DESIRED N3-CTV	31
CHAPTER 4 – BENZYNE CLOSURE	50
CHAPTER 5 – DERIVATIVES OF N3-CTV AND FUTURE WORK	69
Demethylation	69
Apex Functionalization and Metal Coordination	71
CHAPTER 6 – EXPERIMENTAL	78
APPENDIX A – SUPPLEMENTAL DATA	104
BIBLIOGRAPHY	210
VITA	217

LIST OF SCHEMES

Scheme 1 – General Look at the Convergent Trimerization	15
Scheme 2 – Synthesis of Triaza[1,3]meta Cyclophane Reported by Tanaka	16
Scheme 3 – Attempted Trimerization of o-Iodoaniline	16
Scheme 4 – Convergent Trimerization of N-Methyl-2-Bromoaniline	21
Scheme 5 – Two Possible [2x1] Convergent Syntheses	22
Scheme 6 – [2x1] Convergent Synthesis of 2,2'-Dibromodiphenylamine	25
Scheme 7 – Synthesis of 2,2'-Diaminodiphenylamine	25
Scheme 8 – Reduction of N-Methyl-2,2'-Dinitrodiphenylamine	26
Scheme 9 – Attempted Direct Synthesis of the Carbon-Capped N3-CTV	30
Scheme 10 – Linear Retrosynthetic Approach to N3-CTV	31
Scheme 11 – Four Possible Synthetic Strategies Beginning with Chlorine and Building Towards Aniline	32
Scheme 12 – Four Possible Synthetic Strategies Beginning with Aniline and Building Towards Chlorine	33
Scheme 13 – Synthesis of Compound 17 (Intermediate A)	35
Scheme 14 – Methylation and Reduction of Intermediate A	36
Scheme 15 – Synthesis of Compound 20 , Triarylamine B	40
Scheme 16 – Methylation and Reduction of Triarylamine Derivative B	41

Scheme 17 – Complete Linear Synthesis of N,N'-Dimethyl N3-CTV	48
Scheme 18 – Attempted Synthesis of N3-CTV with Bromine Substituent	49
Scheme 19 – Formation of a Benzyne Intermediate Through a Zwitterion	51
Scheme 20 – Proposed Mechanism of the Benzyne Cyclization	53
Scheme 21 – Formation of the Methyl-Shifted Phenazine Derivative	54
Scheme 22 – Protection of the Internal Nitrogen with n-Butyl Bromide	57
Scheme 23 – Proposed Mechanism for the Formation of the 6-membered Phenazine Derivative From the N,N'-Dimethyl Derivative	58
Scheme 24 – Linear Synthesis of the Fluorinated Triarylamine 32	60
Scheme 25 – Synthesis of Compounds 34 Fluoro-N-Methyl-N'Butyl Substrate	61
Scheme 26 – Proposed Mechanism for the Formation of the Butyl-Shifted Phenazine Derivative	62
Scheme 27 – Intermolecular Double-Demethylation	63
Scheme 28 – Attempted Dealkylation of the Butyl Protecting Group in the Absence of a Halogen	64
Scheme 29 – Intermolecular vs. Intramolecular Dealkylation	66
Scheme 30 – Proposed Labeling Experiment to Determine if the Alkyl-Shift is Intra- or Intermolecular	67
Scheme 31 – Attempted Demethylation of N,N'-Dimethyl N3-CTV	70
Scheme 32 – Synthesis of the Trimethyl N3-CTV Derivative	72
Scheme 33 – Proposed Electrophilic Aromatic Substitution of N3-CTV	75

LIST OF FIGURES

Figure 1 - Crown and Saddle CTV	4
Figure 2 – Crown and Saddle CTV-oxime Derivatives	5
Figure 3 – Heterocyclic CTV Derivatives	7
Figure 4 – Structure of TACN and Carbon-Capped TACN Derivative	8
Figure 5 – Structure of C-NETA	9
Figure 6 – Structure of Target Molecule - N3-CTV	10
Figure 7 – Synthetic Approaches to N3-CTV	13
Figure 8 – Oxidative Addition/Reductive Elimination Mechanism	14
Figure 9 – Derivatives of Compound 22a	42
Figure 10 – N,N-Dimethyl N3-CTV	44
Figure 11 – X-ray Structure of N,N-Dimethyl N3-CTV with Atom Labels, Thermal Ellipsoids are at the 50% Probability Level	45
Figure 12 – Crystal Structure of the Methyl-Shifted Phenazine Derivative HCl Salt	55
Figure 13 – Possible Structure of Lithium-Ligated Species	71
Figure 14 – Structures of Gd-Complexing MRI Contrast Agents	73
Figure 15 – Structure of Dimeric Molecular Tweezers	76

LIST OF TABLES

Table 1 – Attempted Convergent Trimerization Utilizing Buchwald-Hartwig Pd-Catalyzed Cross-Coupling Conditions	18
Table 2 – Attempted Convergent Trimerization Utilizing Ullmann Cu-Catalyzed Cross-Coupling Conditions	20
Table 3 – Attempted [2x1] Convergent Synthesis of 2,2'-Dibromodiphenylamine and o-Phenylenediamine	24
Table 4 – Attempted [2x1] Convergent Synthesis of 2,2'-Diaminodiphenylamine and N-Methyl-2,2'-Diaminodiphenylamine	28
Table 5 – Synthesis of Diphenylamine Derivatives, Intermediate A	34
Table 6 – Attempted Reductions of Intermediate A	37
Table 7 – Synthetic Strategies for the Formation of Triarylamine B	39
Table 8 – Attempted Final Cyclization Utilizing Buchwald-Hartwig Conditions	43
Table 9 – Attempted Benzyne Cyclization to N3-CTV	65

LIST OF ABBREVIATIONS

N3-CTV – tribenzo-1,4,7-triazacyclononatriene

CTV – cyclotrimeratrylene

DMSO – dimethyl sulfoxide

TACN – 1,4,7-triazacyclononane

NMR – nuclear magnetic resonance

MRI – magnetic resonance imaging

Ca^{2+} - calcium ion

K^{+} - potassium ion

Lu (III) –lutetium

Bi (III) – bismuth

RIT – radioimmunotherapy

DNA – deoxyribonucleic acid

Cu (II) – copper(II)

$\text{Pd}(\text{dba})_2$ – bis(dibenzylideneacetone)palladium(0)

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

$\text{Pd}(\text{OAc})_2$ – palladium(II) acetate

$\text{P}(\text{t-Bu})_3$ – tri-*t*-butylphosphine

NaOtBu – sodium *tert*-butoxide

KOtBu – Potassium *tert*-Butoxide

CuI – copper(I) iodide

K_2CO_3 – potassium carbonate

Cs_2CO_3 – cesium carbonate

Na_2CO_3 – sodium carbonate

Na_2SO_4 – sodium sulfate

THF – tetrahydrofuran

MeI – iodomethane

n-BuLi – *n*-butyllithium

TLC – thin layer chromatography

SM – starting material

rt – room temperature (25°C)

$\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ – hydrazine hydrate

EtOH – ethanol

MeOH – methanol

Pd/C – palladium(0) on Carbon

KOH – potassium hydroxide

Me_2SO_4 – dimethyl sulfate

NaH – sodium hydride

KH – potassium hydride

AcCl – acetyl chloride

S_NAr – nucleophilic aromatic substitution

tol – toluene

Cu₂O – copper(I) oxide

DMF – N,N'-dimethylformamide

CuCl – copper(I) chloride

KBH₄ – potassium borohydride

H₂ – molecular hydrogen

S_N2 – bimolecular nucleophilic substitution

SnCl₂ – tin(II) chloride

HCl – hydrochloric acid

HBr – hydrobromic acid

RaNi – raney nickel

atm – atmosphere

psi – pounds per square inch

(SIPr)Pd(Cin)Cl – Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2,6-di-i-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II)

TOFMS – time of flight mass spectrometry

MW – microwave

LUMO – lowest unoccupied molecular orbital

N₂ – molecular nitrogen

CO₂ – carbon dioxide

KDA – potassium diisopropylamine

DIPA – diisopropylamine

LAH – lithium aluminium hydride

AcOH – acetic acid

Li – lithium

EAS – electrophilic aromatic substitution

Pd – palladium

Gd – gadolinium

NR – no reaction

Xyl – xylene

PE – petroleum ether

EA –ethyl acetate

DCM – dichloromethane

Et₂O – diethyl ether

ABSTRACT

Supramolecular chemistry involves the formation of complex molecular entities that have the capacity to participate in specific molecular recognition of guest molecules. A commonly employed scaffold in supramolecular chemistry is the trimeric crown-shaped molecule cyclotrimeratriylene (CTV). CTV has been studied extensively for its capability of binding a number of smaller organic and organometallic guests within its bowl-shaped cleft and has been used as a building block enabling the construction of more complex cryptophanes. The goal of this research is the synthesis and characterization of a novel cyclophane, tribenzo-1,4,7-triazacyclononene and derivatives thereof. These new cyclophanes should have greater versatility than the parent hydrocarbon macrocycle including greatly enhanced water solubility, ability to coordinate to metal ligands, the potential for use in drug delivery, and unique optical and liquid crystal properties. Progress towards these molecules have employed both Buchwald-Hartwig palladium catalyzed N-arylation as well as benzyne chemistry. The synthesis of tribenzo-1,4,7-triazacyclononatriene and its derivatives will be discussed.

CHAPTER 1
AN INTRODUCTION TO SUPRAMOLECULAR CHEMISTRY,
CTV AND N3-CTV

Supramolecular Chemistry

The area of supramolecular chemistry is of continued interest due to a wide variety of applications including materials technology, catalysis, medicine, analytical detection and sensing. Supramolecular chemistry involves the formation of complex molecular entities that have the capacity to participate in specific molecular recognition of guest molecules.^{1,2} Host-guest chemistry is the result of weak non-covalent interactions between molecules such as hydrogen-bonding, metal coordination, hydrophobic forces, π - π interactions and van der Waals forces. These types of interactions result in the complementarity of the host and guest molecules. Complementarity is well established in biology and is critical to both structure and function of many biological processes including protein folding, the binding of substrates to enzymes, and DNA base pairing of the double helix structure.³ Supramolecular host-

guest chemistry is often studied with the intention of gaining a better understanding of biological processes and mimicking those processes.

Cyclophanes

Cyclophanes are supramolecular structures comprised of aromatic units with bridging chains that may be used to form cage-like structures,⁴ and have applications in molecular and receptor recognition. They have also been used as building blocks for organic catalysts as well as in the preparation of crown ethers and cryptands.⁵ The cyclophane motif exists in nature, for instance the natural product cavitularin, a metacyclophane. Recent advances in the synthesis of cyclophanes include Haouamine A, which is a paracyclophane found in certain species of tunicate, and is of interest for its use as a potential anticancer drug.^{6,7} Other biological and pharmaceutical uses for cyclophanes include reversal agents of muscle relaxants⁸ and water soluble inhibitors of HIV protease.⁹

Host-guest chemistry can involve the binding of cations, anions, metals or neutral molecules, all through non-covalent interactions. The binding of metal cations plays a significant role in biology; for example, the naturally occurring antibiotic valinomycin binds K^+ and transports it through the mitochondrial membrane in the presence of Na^+ ions. The K^+ is held tightly in the center of the molecule by complexation to the electronegative oxygen atoms of the ester groups while the macrocycle itself is stabilized by H-bonding.³ Many enzymatic binding sites contain catalytic metal cations that are involved in the regulation of concentration gradients across membranes. Recently, metal cations like Gd^{3+} have been used in MRI contrast agents. Porphyrins are an example of

naturally occurring macrocycles that bind iron in heme groups and magnesium in chlorophyll.³ Furthermore, host molecules that are capable of binding specific metal-cation guests can be utilized in the removal of toxins from poisoning victims and pollutants from the environment.³

Supramolecular chemistry involving the specific binding of anionic guests is of significant interest biologically and environmentally.³ The binding of a negatively-charged guest can be very strong and selective. Binding of anions may also alter the reactivity of the receptor molecule. Anions are extremely important in biology, for instance many enzyme substrates are negatively charged species. Anions can also play significant roles in diseases. Cystic fibrosis is a genetic disease that is caused by the misregulation of chloride channels.

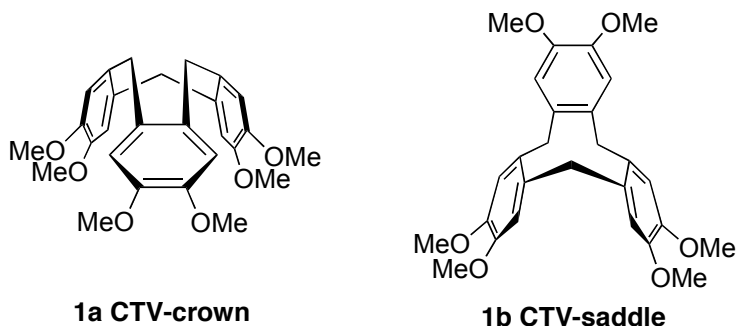
The study of supramolecular chemistry can have a significant impact across multiple disciplines, and there continues to be great interest in the development of cyclophanes as hosts for ionic guests.¹⁰⁻¹⁵ For example, Zhang and coworkers were investigating negatively charged cyclophanes for chelation of quaternary ammonium neuromuscular blocking agents,⁸ while bis-quinolinium cyclophanes were shown to be effective inhibitors of small conductance Ca^{2+} activated K^{+} channels.^{16, 17} The design and synthesis of cyclophanes capable of ionic binding continues to be challenging, especially for binding of anions. There are many factors that one must account for when designing synthetic receptors for ionic guests: size, charge, pH and solvation will have an impact on the binding of the guest molecule to the receptor. Another challenge is the solubility of the synthetic receptors. Biological processes occur in an aqueous environment and

synthetic receptors are often insoluble in water. One challenge facing supramolecular chemistry is the design and synthesis of synthetic receptors that are soluble in an aqueous media.¹⁸

Cyclotrivenylene (CTV)

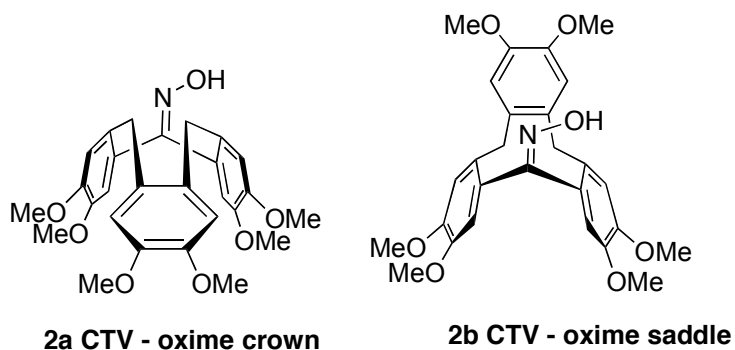
Cyclotrivenylene (CTV, **1a**, **1b**), a [1.1.1]orthocyclophane, is an archetypal cyclophane scaffold that is commonly employed in supramolecular chemistry.¹⁹ CTV is readily prepared from veratryl alcohol in acid and has been studied extensively for its capability of binding a number of smaller organic and organometallic guests within its bowl-shaped cleft.²⁰⁻²² CTV modification continues to be a significant area of study.²³⁻²⁷ Nierengarten reported the encapsulation of C₆₀ by dendritic CTV derivatives,²³ while Kuck and coworkers reported a carbon-capped CTV derivative.²⁴ Furthermore, Hardie has synthesized many CTV derivatives, including those containing pyridyl functional groups for use as multifunctional ligands in coordination networks,²⁵ CTV combined with halogenated carboborane and Group 1 metal cations²⁶ as well as the characterization of CTV clathrates with ethanol and DMSO.²⁷

FIGURE 1 - Crown and Saddle CTV



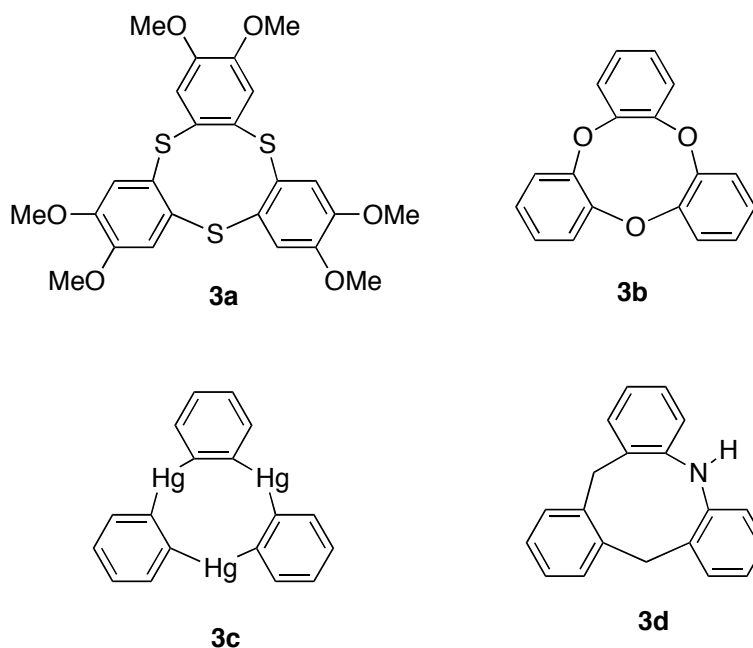
CTV exists almost exclusively in the crown conformation **1a**. Recently, Zimmermann and coworkers isolated and characterized the saddle conformer of CTV **1b** through high-temperature melt and quench techniques, and also studied the thermodynamic and kinetic properties of the interconversion between the crown and saddle CTV conformers.²⁸ We have successfully isolated the crown **2a** and saddle **2b** conformers of CTV-oxime derivative,²⁹ and studied the kinetics and thermodynamics of interconversion between the crown and saddle conformers,³⁰ as part of our interest in exploration of apex-modified CTV derivatives.³¹

FIGURE 2 - Crown and Saddle CTV-oxime Derivatives



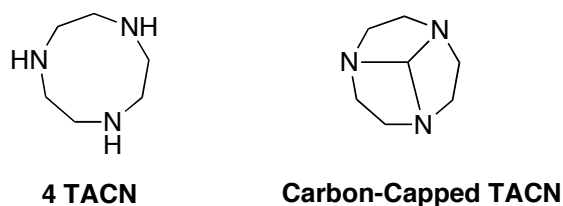
CTV is often used as a building block enabling the construction of more complex cryptophanes,³²⁻³⁵ which is one reason for continued interest in the elaboration of CTV.³⁶ Collet was among the first to transform CTV by dealkylating the six methoxy groups followed by treatment with bromoacetate esters and subsequent ester hydrolysis to obtain the slightly water soluble hexa-acid cyclophanes.³⁷ Huber and Nierengarten have both reported on the synthesis of water-soluble CTV cryptands; Huber substituted the methoxy groups for an acetic acid moiety which led to a new class of xenon-carrier

molecules that are soluble in water at physiological pH,^{38,39} while Nierengarten has appended multiple polyethylene glycol units to the periphery of CTV in order to enable the hydrophobic core to dissolve in water and solublize C₆₀.⁴⁰ Furthermore, there are several heteroatom derivatives of CTV and the corresponding tribenzocyclononene core in which the methylene groups have been replaced with sulfur, oxygen, mercury and nitrogen (**3a-d**).⁴¹⁻⁴³ Trithiacyclotrivenylene **3a**^{44,45} forms complexes with copper(I),⁴⁶ rhodium (III),⁴⁷ and platinum (II),⁴⁸ and it also exists in a temperature and solvent-dependent equilibrium of the crown and saddle forms. In addition, the trioxacyclononene **3b**,^{41,42} and trimercury **3c**,⁴³ which is planar rather than crown-shaped, have also been reported. In 2005, Hara and co-workers reported the first nitrogen-substituted cyclophane with the synthesis of monoamine tribenzo-1-azacyclophane **3d** which was prepared as a potential benzodiazepine receptor ligand.⁴⁹ Azacyclophane **3d** was thus designed to act as a guest (ligand) to the benzodiazepine receptor whereas **3a-3c** were designed as host molecules.

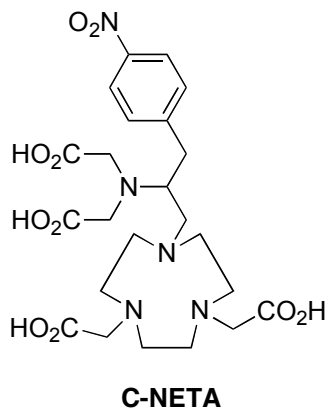
FIGURE 3 - Heterocyclic CTV Derivatives**1,4,7-Triazacyclononane (TACN)**

The small macrocycle 1,4,7-triazacyclononane (TACN, **4**) is a highly symmetrical tridentate ligand that has been shown to bind multiple metal guests, including zinc,⁵⁰ copper,⁵¹ cobalt and nickel.⁵² TACN is easily prepared from ethylenediamine; and several derivatives have been reported in the literature, including the carbon-capped orthoamide (Figure 4).⁵³ In addition to metal chelating properties, TACN has been functionalized on nitrogen with a variety of groups enabling physicochemical and functional tuning of the molecular properties.⁵⁴

FIGURE 4 - Structure of TACN and Carbon-Capped TACN Derivative



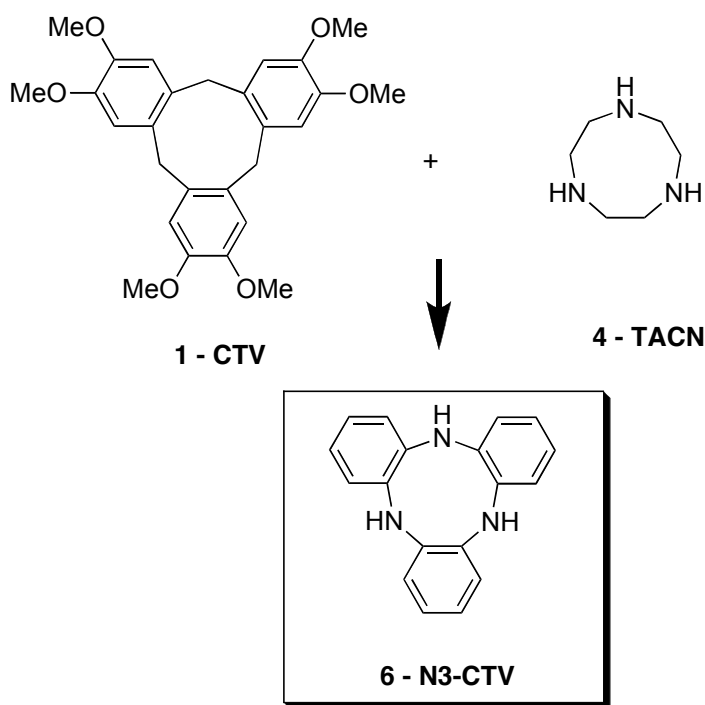
Several biological uses of TACN derivatives have been reported, including gadolinium complexes which are of interest as MRI contrast agents.^{55, 56} In addition, TACN derivatives have been of interest for antibody-targeted radiation therapy (radioimmunotherapy, RIT). RIT utilizes bifunctional ligands that can tightly bind a cytotoxic metal as well as a tumor-specific antibody. Brechbiel and co-workers have recently reported the synthesis of C-NETA, a derivative that has shown rapid binding of Lu(III) and Bi(III) (Figure 5).⁵⁷

FIGURE 5 - Structure of C-NETA

Furthermore, N-functionalized complexes of TACN have been shown to form bis-complexes with Cu(II) which have been used as DNA-delivery systems,⁵⁸ and a TACN derivative with guanidinium and hydroxyl side-arms has shown to be a very efficient at promoting DNA cleavage.⁵⁹

Tribenzo-1,4,7-triazacyclononatriene (N3-CTV)

The goal of this research is the synthesis of target molecule tribenzo-1,4,7-triazacyclononatriene (N3-CTV, **6**), a structural combination of the CTV and TACN molecules (Figure 6).

FIGURE 6 - Structure of Target Molecule - N3-CTV

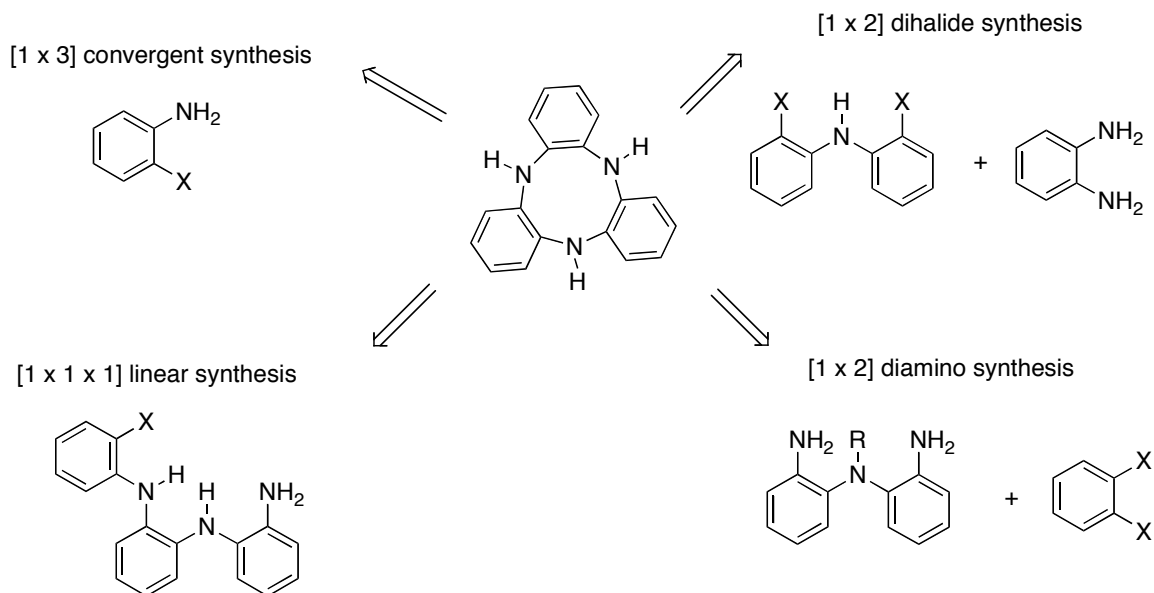
N3-CTV should have much greater versatility than the parent CTV including enhanced water solubility due to the three apex nitrogens. In addition to enhanced water solubility the apex nitrogens may also aid in the binding of charged guests. Polyaza macrocycles can incorporate both electrostatic interactions and hydrogen bonding enabling the receptor to be tuned;³ the potential ability of N3-CTV to bind cationic species or a proton in its apex in the crown conformation should yield a charged host with the potential of binding anionic guests. N3-CTV and its derivatives may have medicinal applications, for example

the biological delivery of fullerenes. Most modifications of the parent CTV has been accomplished along the periphery of the molecule; a significant advantage offered by the target N3-CTV is the ability to modify the cyclophane at the apex nitrogens enabling the physiochemical properties of the cyclophane to be modified. Additionally, the apex nitrogens can serve as ligands for metal coordination. Attachment of the appropriate side-arm to one or more of the apex nitrogens can enable the N3-CTV cyclophane to be bound to solid surfaces, for instance gold or gold nanoparticles. Coordination of the N3-CTV with different metals including gadolinium may be of interest as MRI contrast agents or RIT drug candidates. The new triazacyclononene and its derivatives may also be studied for their unique liquid crystal properties, which can have optical and electronic applications. N3-CTV has the potential to be utilized in multiple areas of chemistry including materials technology, medicine, analytical detection and sensing.

CHAPTER 2

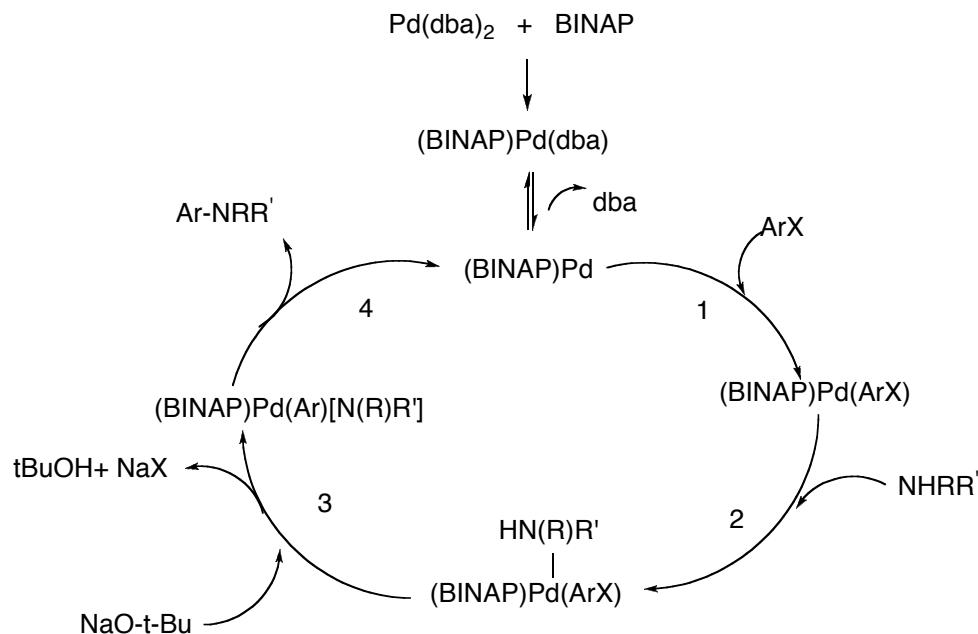
ATTEMPTED CONVERGENT SYNTHESSES OF N3-CTV

The desired target, N3-CTV is a 9-membered cyclophane comprised of three aniline groups bonded together through N-aryl bonds. Looking at the N3-CTV compound retrosynthetically, one can envision four different synthetic approaches as shown in the figure below. The simplest method for synthesizing N3-CTV would be a direct [1x3] convergent trimerization. Here, a simple o-substituted aniline would react with itself generating the desired cyclophane in a one-pot reaction. One could also take advantage of a [2x1] convergent synthesis in which the third aromatic ring would be joined in a double N-arylation reaction. Finally, N3-CTV may be synthesized one ring at a time in a linear approach, which is the approach that was ultimately realized.

FIGURE 7 – Synthetic Approaches to N3-CTV

A key N-arylation reaction in the pursuit of the novel triaza-CTV (N3-CTV) takes advantage of a metal-catalyzed oxidative addition/reductive elimination mechanism. Conditions for palladium-catalyzed N-arylation have been established by Buchwald⁶⁰⁻⁶² and Hartwig.⁶³⁻⁶⁶

The catalytic cycle of the Buchwald-Hartwig N-arylation is illustrated in Figure 8. The catalyst and ligand combine to form the active Pd-phosphine complex. This complex then oxidatively inserts into the aryl-halide bond. Next the nitrogen of the amine bonds to the palladium, then the amine is deprotonated by base. Finally the C-N bond is formed by reductive elimination along with regeneration of the Pd-phosphine complex.

FIGURE 8 - Oxidative Addition/Reductive Elimination Mechanism

The Pd-phosphine complex is very important in these cross-coupling reactions because of the “natural bite angle” of the P-Pd-P angle.⁶⁷ In general, Pd(II) prefers a square planar geometry because they are d^8 whereas Pd(0) complexes will coordinate in linear, tetrahedral and trigonal geometries because Pd(II) complexes are d^{10} .⁶⁷ Thus the choices of palladium catalyst and phosphine ligand are extremely important. If during oxidative insertion, the Pd(II) species is present, then a bond formation must complement a square planar geometry. On the other hand, if the Pd(0) species is present, more options for coordination geometry may lead to C-N bond formation in a greater variety of substituents. In addition to the Pd-catalyzed Buchwald-Hartwig conditions the familiar copper-mediated Ullmann reaction has been studied in detail,⁶⁸ and a milder set of

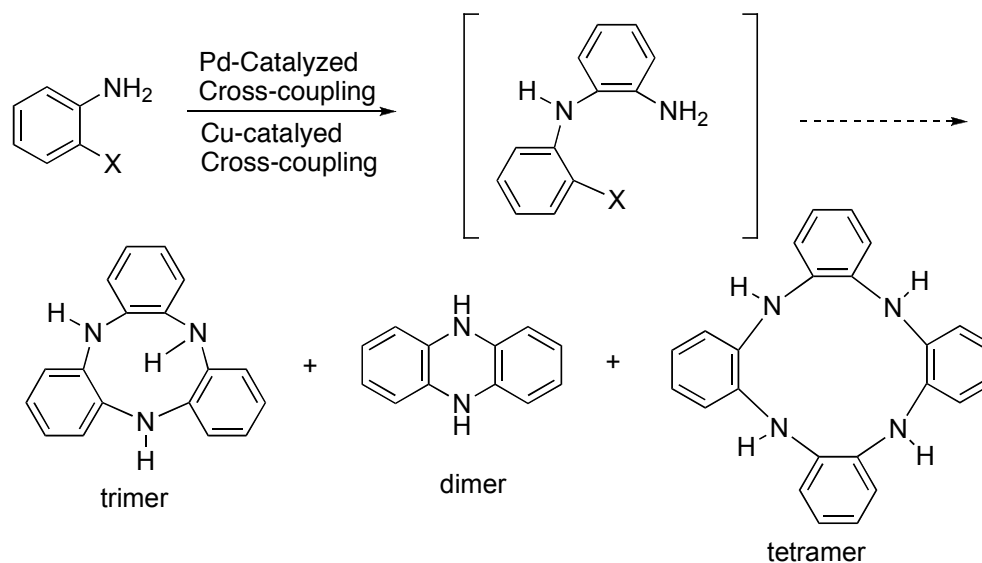
copper-catalyzed Ullmann conditions described by Zhang have also been applied.⁶⁹

Similar to palladium (0), copper can coordinate in linear or tetrahedral geometry. The different metals offer different reactivities, thus creating more variety for synthetic approaches leading to the target N3-CTV.

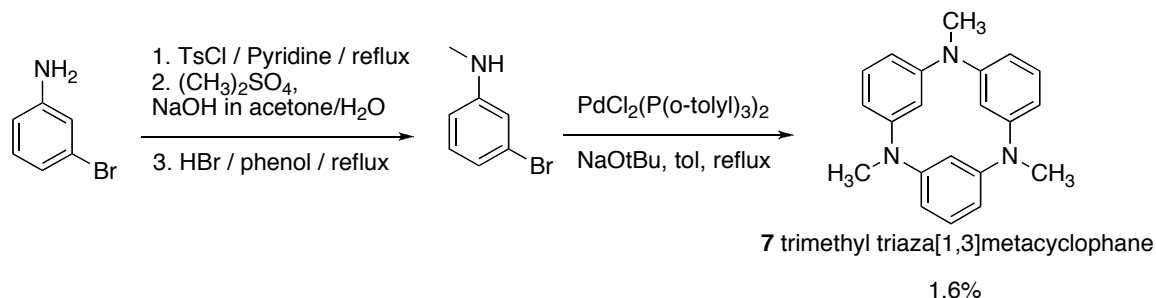
Convergent Trimerization

The simplest and most direct method involves the convergent trimerization of an ortho-substituted halogenated aniline. In addition to the desired trimer, the dimer, tetramer as well as higher oligomers are also possible (Scheme 1).

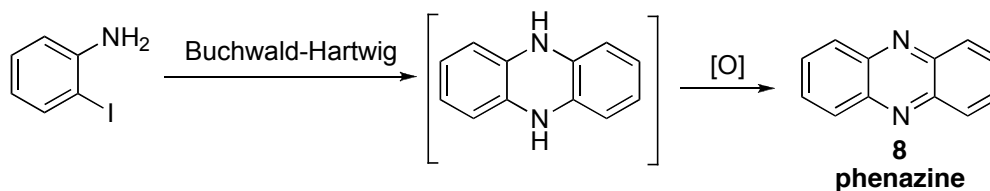
SCHEME 1 - General Look at the Convergent Trimerization



This route has precedent in the work of Tanaka and coworkers who described the synthesis of trizaza[1,3]meta cyclophane **7** in 1.6% yield⁷⁰ via direct trimerization of N-methyl-3-bromoaniline utilizing the palladium catalyzed cross-coupling methods of Buchwald and Hartwig (Scheme 2).







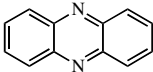


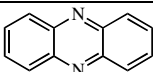


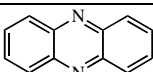
SCHEME 2 - Synthesis of Triaza[1,3]meta Cyclophane Reported by Tanaka

We initially attempted to synthesize our target triaza orthocyclophane using similar methods to that of Tanaka. First, we subjected 2-iodoaniline to Buchwald-Hartwig cross-coupling conditions employing Pd(OAc)₂ as the catalyst, P(t-Bu)₃ as the ligand, and NaOtBu as the base in refluxing 1,4-dioxane under an inert atmosphere (Scheme 3). These conditions afforded phenazine **8** in 92% isolated yield, apparently via facile air oxidation of the metastable dihydrophenazine,⁷¹ as the only detected product confirmed by ¹H NMR (δ 8.25 and 7.83).

SCHEME 3 – Attempted Trimerization of o-Iodoaniline

N-Arylation via Pd-catalysis may be accomplished using numerous choices for the catalyst, ligand, base and solvent employed. The different components of the Buchwald-Hartwig reactions can lead to countless possibilities in the pursuit of a particular reaction sequence. For example, the phosphine ligands can be either mono-dentate or bidentate, there have been several different reports on what type of ligand best complements particular catalysts, halides and amines.⁷²⁻⁷⁵ There have also been several accounts of different catalytic systems examining which are better for specific arylations and also limitations of specific systems.^{61, 76-82} In addition, numerous ligands have been synthesized in order to decrease the time and temperature required for reactions to go to completion.^{63, 83, 84} A variety of combinations of catalysts and ligands were employed in an attempt to obtain the desired triaza-cyclophane in a convergent trimerization (Table 1). When DPEPhos was used as the ligand, no reaction was observed (Table 1, entries 1 and 2). A trace of phenazine was formed when $P(t-Bu)_3$ was used as the ligand; the recovery of SM was most likely the result of improper handling of the $P(t-Bu)_3$ reagent (Table 1, entry 3). The use of KOtBu as a base over NaOtBu resulted in 43% isolated yield of phenazine in addition to recovered SM. Despite several different attempts, phenazine was the only isolated product for this convergent trimerization approach under Pd-catalyzed cross-coupling conditions.

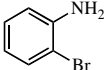
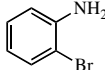
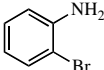
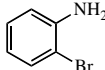
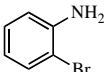
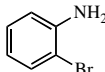
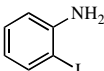
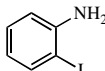
TABLE 1 - Attempted Convergent Trimerization Utilizing Buchwald-Hartwig Pd-Catalyzed Cross-Coupling Conditions

ArX	ArNH	Catalyst	Ligand	Base	Solvent	Temp(°C)	Product
		Pd(OAc) ₂	DPEPhos	NaO-t-Bu	Toluene	111/24 h	N/R
		Pd(OAc) ₂	DPEPhos	NaO-t-Bu	Toluene	160/24 h	N/R
		Pd(OAc) ₂	P(t-Bu) ₃	NaO-t-Bu	Toluene	111/2 h	 trace
		Pd(OAc) ₂	P(t-Bu) ₃	NaO-t-Bu	Dioxane	130/3 h	 92%
		Pd(OAc) ₂	P(t-Bu) ₃	KO-t-Bu	Toluene	125/3 h	 43%

In addition to Buchwald and Hartwig methods, copper-catalyzed Ullmann conditions were also explored in the attempted convergent trimerization toward N3-CTV. The overall reaction mechanism for copper-mediated catalysis is the same as that of palladium; a catalyst-ligand complex oxidatively inserts into the aryl halide bond, which is followed by nucleophilic attack of the aniline nitrogen, deprotonation by a base and

finally reductive elimination of the desired product containing the newly formed C-N bond. Reaction conditions for copper-catalyzed N-arylation involve a copper (I) catalyst such as CuI, an amino acid ligand such as L-proline, and a base. Zhang and coworkers employed Ullmann conditions in order to obtain an azametacyclophane;⁸⁵ similarly we employed CuI, L-proline and K₂CO₃ in DMSO. The desired cyclophane was not isolated under attempted Cu-catalysis (Table 2). Only starting material was recovered using purchased CuI (Table 2, entry 3), probably due to its prolonged exposure to light and air. When freshly prepared CuI was used, no reaction occurred and starting material was recovered (Table 2, entries 1,2 and 4), even though a standard reaction with 1-bromo-4-chlorobenzene and aniline showed product spots by TLC analysis.

TABLE 2 - Attempted Convergent Trimerization Utilizing Ullmann Cu-Catalyzed Cross-Coupling Conditions

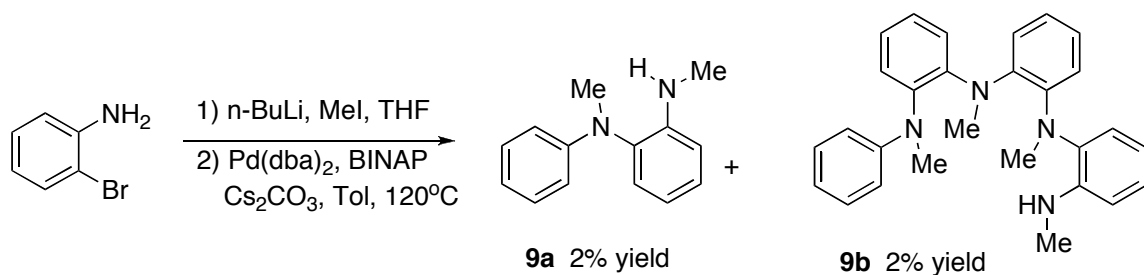
ArX	ArNH	Catalyst	Ligand	Base	Solvent	Temp(°C)/ Time	Product
		CuI (ap-67-1)	L-Pro	K ₂ CO ₃	DMSO	95/24 h 130/24 h	N/R
		CuI (ap-71-1)	L-Pro	K ₂ CO ₃	DMSO	100/ 40 h 160/24 h	N/R
		CuI (Aldrich)	L-Pro	K ₂ CO ₃	DMSO	100/40 h	N/R
		CuI (ap-71-1)	L-Pro	K ₂ CO ₃	DMSO	125/24 h 160/24 h	N/R

*ap1-67-1 and ap1-71-1¹²⁴

The results of the attempted convergent trimerization were consistent with those of Tanaka who was unable to obtain the unalkylated (tris-NH) triaza metacyclophane from the cross-coupling reaction using a primary aniline.⁷⁰ Bearing this in mind, we then tried using a secondary aniline. 2-Bromoaniline was methylated employing n-BuLi followed by quenching with MeI in THF. The N-methyl 2-bromoaniline was subjected to cross-coupling conditions involving Pd(dba)₂ as the catalyst, racemic BINAP as the ligand, and Cs₂CO₃ as the base. The reaction was run in dry toluene for 24-48 hours at 120°C. I isolated the reduced dimer **9a**, 0.3% of the theoretical yield, and what we believe is the unclosed tetramer **9b** in 2% yield (**9b**) (Scheme 4). There is also an additional 10 mg, (2%

yield) of a mixture of 2 unknown products that are likely oligomers and not phenazine derivatives nor the desired N3-CTV. NMR data of the reaction mixture from the attempted convergent trimerization of N-methyl-2-bromoaniline were compared to the authentic standards of both the trimethyl N3-CTV derivative and dimethyl N3-CTV derivative, both of which were successfully synthesized later by alternative methods. The attempted convergent trimerization of N-methyl-2-bromoaniline showed no indication of the presence of either trimethyl or dimethyl N3-CTV derivatives. Although the desired N3-CTV was not obtained through this synthetic route, the isolation of oligomeric products other than phenazine was an indication of some progress.

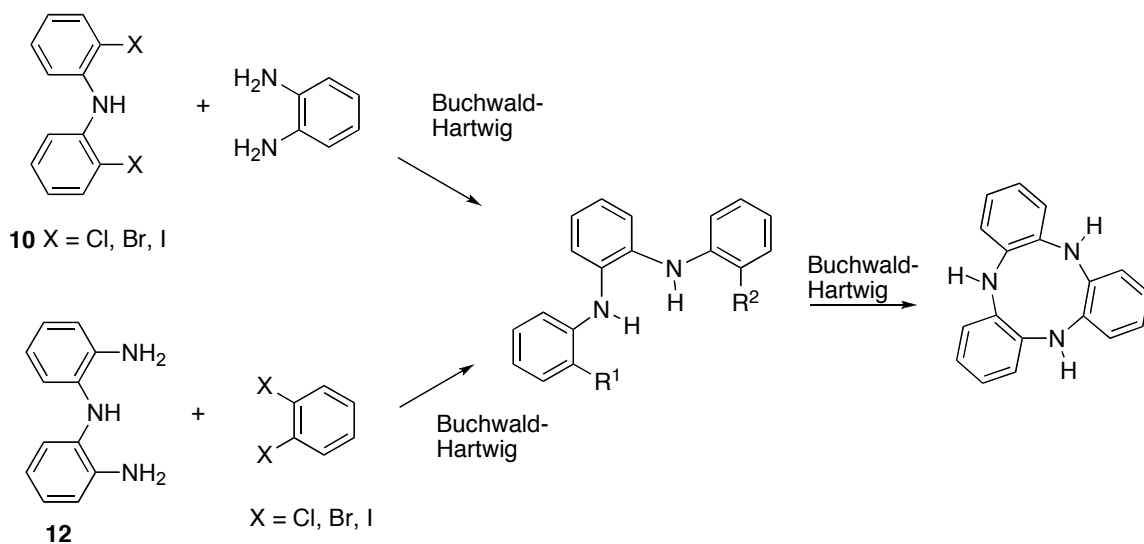
SCHEME 4 - Convergent Trimerization of N-Methyl-2-Bromoaniline



[2x1] Dihalide Convergent Synthesis

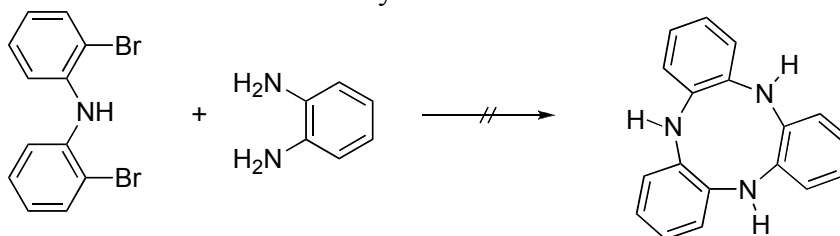
When the desired product was not detected through the convergent trimerization, efforts were focused on a [2x1] synthetic approach. Here, the synthesis could begin with either a 2,2'-dihalodiphenylamine **10** or a 2,2'-diaminodiphenylamine **12**, both of which could potentially undergo a double N-arylation via Buchwald-Hartwig or Ullmann coupling with the appropriate benzene derivative (Scheme 5). It was hypothesized that the formation of the first C-N bond would give rise to more entropically favorable ring closure conditions for the second C-N bond through an intramolecular C-N bond formation.

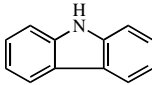
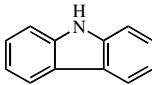
SCHEME 5 - Two Possible [2x1] Convergent Syntheses



Initial attempts to synthesize N3-CTV via the [2x1] convergent approach began with 2,2'-dibromophenylamine and o-phenylenediamine. Both palladium and copper-catalyzed conditions were employed for the attempted convergent synthesis (Table 3). Most of the synthetic conditions employed showed no reaction based on thin layer chromatography (TLC) analysis (Table 3, entries 1-4). However, when Buchwald-Hartwig conditions consisting of Pd(dba)₂, BINAP and NaOtBu were employed, the major product formed and isolated was carbazole which was confirmed by ¹H NMR (δ 8.05 bs) (Table 3, entries 5 and 6). Carbazole is the result of reductive coupling of the dihalide to produce the aryl C-C bond.

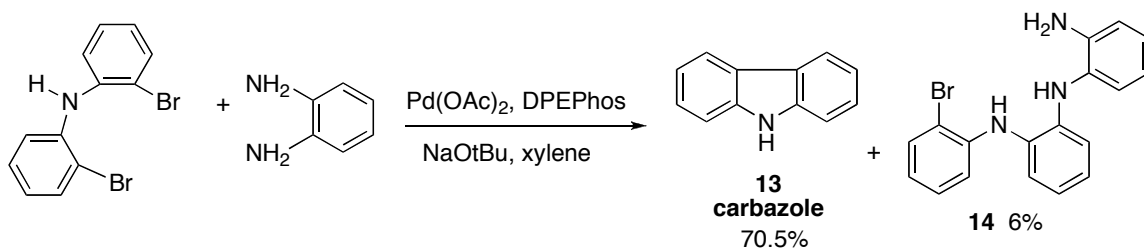
TABLE 3 - Attempted [2x1] Convergent Synthesis of 2,2'-Dibromodiphenylamine and o-Phenylenediamine



Catalyst	Ligand	Base	Solvent	Time/temp	Product
Pd(OAc) ₂	P(t-Bu) ₃	NaO-t-Bu	toluene	80/30 min	recovered
				111/48 h	SM
Pd(OAc) ₂	DPEPhos	NaO-t-Bu	toluene	80/30 min	recovered
				111/48 h	SM
CuI	L-Pro	K ₂ CO ₃	DMSO	85/24 h	recovered
				150/24 h	SM
Pd(OAc) ₂	DPEPhos	NaO-t-Bu	dioxane	80/30 min	recovered
				120/5 d	SM
Pd(dba) ₂	BINAP	NaO-t-Bu	toluene	80/30 min	 6%
				120/48 h	
Pd(dba) ₂	BINAP	NaO-t-Bu	p-xylene	80/30 min	 70.5%
				138/48 h	

In addition to carbazole **13**, the mono-coupled triaryl product **14** was also isolated in 6% yield along with 22% recovered SM (Scheme 6).

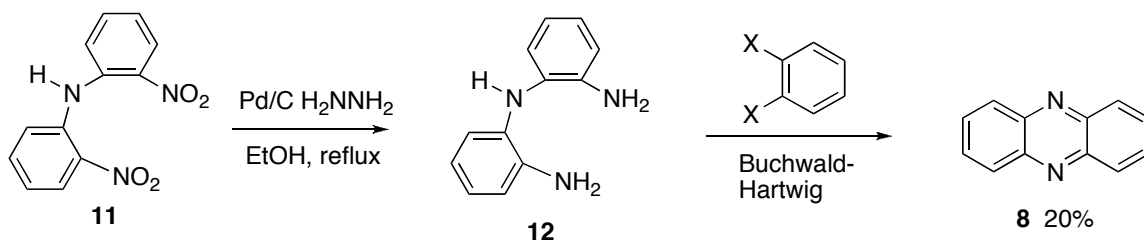
SCHEME 6 - [2x1] Convergent Synthesis of 2,2-Dibromodiphenylamine



[2x1] Diamino Convergent Synthesis

A parallel [2x1] synthesis beginning with 2,2'-diaminodiphenylamine **12**^{86, 87} was also explored. The 2,2'-diaminodiphenylamine **12** was obtained by reduction of 2,2'-dinitrodiphenylamine **11** with hydrazine hydrate ($\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$) and Pd/C in refluxing EtOH according to the general procedure of Black *et al.*⁸⁷ Compound **12** and 1,2-diiodobenzene were subjected to palladium-catalyzed N-arylation producing phenazine **8** in 20% yield as the only isolated product (Scheme 7). This is a surprising result since it involves an oxidation of the o-dianiline; however, Koutentis showed a similar result when benzene tetraamines were exposed to air in refluxing EtOH.⁸⁸

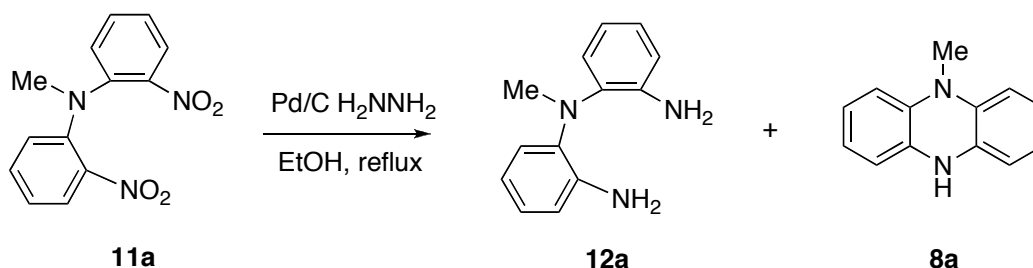
SCHEME 7 - Synthesis of 2,2'-Diaminodiphenylamine



We decided to install a methyl protecting group on the central nitrogen in an

attempt to stop the formation of phenazine during reduction; this was easily accomplished utilizing KOH and Me₂SO₄ in refluxing acetone to give **11a** in quantitative yield.^{89, 90} Reduction of **11a** with H₂NNH₂ and Pd/C led to a 50:50 mixture of the desired N-methyl-2,2'-diaminodiphenylamine **12a** and N-methyl dihydrophenazine **8a**, again a product of oxidation (Scheme 8). This reflects how electron rich the diaminodiphenylamine is due to the electron donating nature of the three nitrogens in the system. Note here that air was carefully excluded, without effect, and we therefore believe that the electron acceptor was the dinitro starting material rather than molecular oxygen.

SCHEME 8 - Reduction of N-Methyl-2,2'-Dinitrodiphenylamine



Thus, in order to try and overcome the formation of phenazine derivatives during reduction, an electron-withdrawing acetyl group was attempted as a protecting group for the nitrogen in order to reduce the electron-rich nature of the molecule and reduce its lability toward oxidation. Protection of the middle nitrogen was attempted unsuccessfully with several different electron-withdrawing groups (Table 4). The

electron-withdrawing nature of the nitro groups on the diphenyldiamine make the secondary amine a very weak nucleophile, even when the protecting group was added to the deprotonated aniline. An acetyl group was successfully added in 50% yield with NaH and AcCl in THF, but was readily lost during purification with column chromatography. The loss of the acetyl group reflects the stability of the diphenylamine as a leaving group. Thus the acyl was too labile to survive Buchwald-Hartwig conditions. Closure to the 9-membered cyclophane was still attempted by N-arylation of N-methyl-2,2'-diaminodiphenylamine **12a** and a 1,2-dichlorobenzene (Table 4). Conditions including Pd-catalyzed N-arylation led to the isolation of starting material, phenazine, or N-methyl dihydrophenazine (Table 4, entries 1 and 2). Also, similar results were observed in the attempted N-arylation of the 2,2'-diaminodiphenylamine with Cu-catalysis. We isolated what we believe may be a copper-ligated species (Table 4, entry 5) based on two broad singlets in the aromatic region, presumably the two NH's (δ 7.07 and δ 6.43), however the symmetry of the molecule suggest otherwise.

In addition to metal-catalyzed cross coupling conditions, a double S_NAr (Table 4, entry 5) was employed in the attempted closure of the free diaminoaniline. The 2,2'-diaminodiphenylamine along with 1,2-dichloro-4,5-dinitrobenzene and KOTBu were mixed in refluxing EtOH. The S_NAr conditions led to the recovery of the 1,2-dichloro-4,5-dinitrobenzene and diphenylamine starting materials. A change in solvent and reaction temperature may lead to more favorable reaction conditions. The phenazine and N-methyl dihydrophenazine products were formed easily under Pd-catalyzed cross-

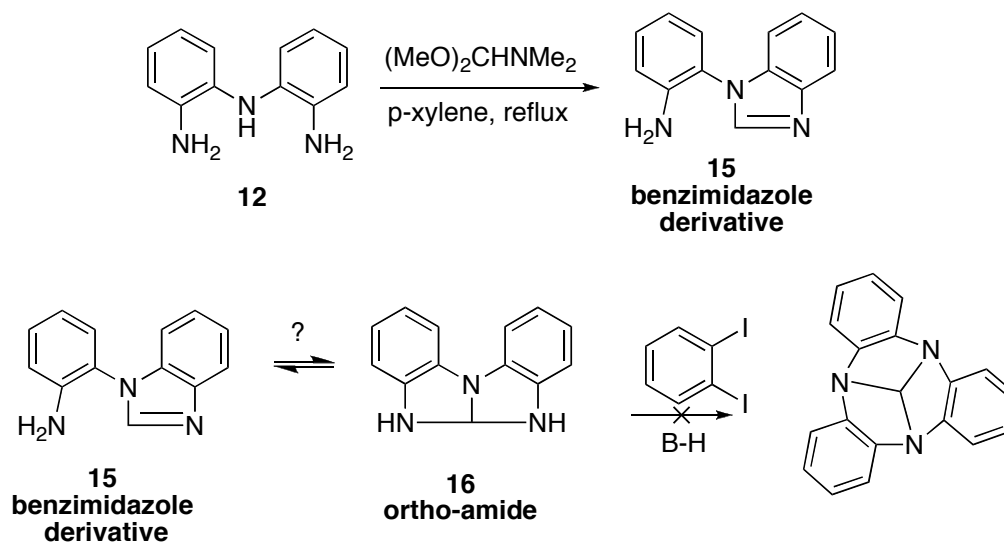
coupling conditions reflecting how labile toward oxidation the system is. Hence we abandoned the approach involving direct reaction of 2,2'-diaminodiphenylamine.

TABLE 4 - Attempted [2x1] Convergent Synthesis of 2,2'-Diaminodiphenylamine and N-Methyl-2,2'-Diaminodiphenylamine

Diamine	Dihalobenzene	Conditions	Products Isolated
		KOtBu / tol 130°C / 24 h	 13% 87% recovered SM
		KOtBu / tol 130°C / 24h	 20% 80%
		Cu ₂ O / DMF reflux 36 h	Products were not identified by ¹ H NMR
		Copper Powder / CuI, Na ₂ CO ₃ DMF, 120°C 48h	 2% 3% 6%
		EtOH, KOtBu double S _N AR	 recovered SM

Templated Convergent Synthesis

One other convergent route explored the idea of forming a template in which the overall structure of the desired N3-CTV was held in place by a carbon cap similar to the carbon-capped TACN derivative reported by Atkins.⁹¹ Using the general method of Atkins, compound **12** and the dimethyl ortho-amide of DMF were mixed in refluxing p-xylene in the attempted direct synthesis of the carbon-capped ortho-amide (**16**). Only the benzimidazole **15** was isolated based on ¹H NMR analysis, δ 3.67 (2H, bs), δ 7.99 (1H, bs), which we hoped would be in equilibrium with the carbon-capped ortho amide. The equilibrium however appears to be shifted exclusively towards the benzimidazole, believed to be due to the strain in the 5-membered rings of the ortho-amide (Scheme 9).

SCHEME 9 - Attempted Direct Synthesis of the Carbon-Capped N3-CTV

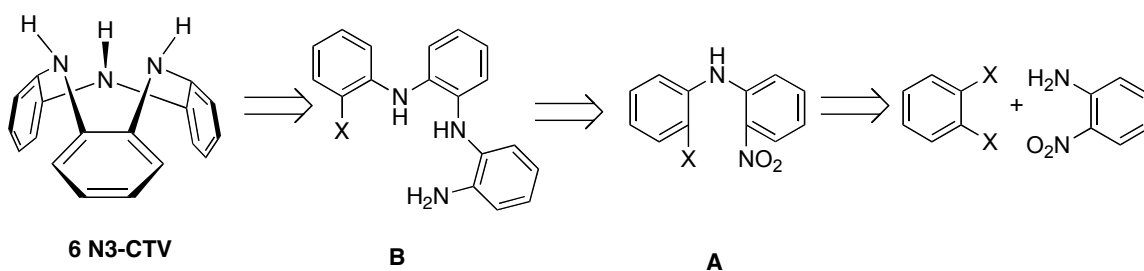
The formation of the desired N3-CTV through a convergent synthesis involving only one or two steps resulted in phenazine and phenazine-like derivatives as the major products isolated. Despite the many different chemical strategies employed, the electron rich nature of the diphenylamine in combination with the ortho-substitution are ideal conditions favoring 6-membered phenazine formation over the desired 9-membered N3-CTV. Therefore a more traditional linear synthetic approach was employed in order to overcome the synthetic challenges of unwanted phenazine by-products.

CHAPTER 3

LINEAR SYNTHETIC STRATEGY AND THE
FORMATION OF THE DESIRED N3-CTV

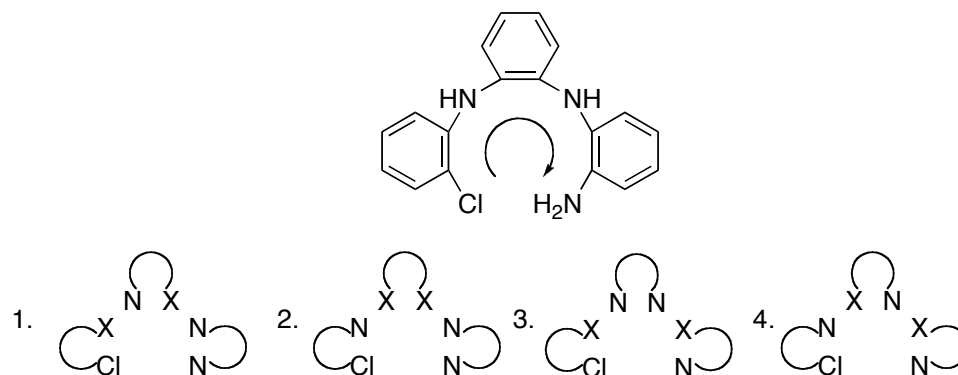
The continual formation of phenazine and phenazine-like by-products isolated utilizing more convergent approaches led to the examination of a linear synthetic strategy. The general retrosynthetic method is outlined in Scheme 10. The desired N3-CTV was constructed one ring at a time enabling protection of the nitrogens along the way, eliminating the formation of unwanted phenazine by-products.

SCHEME 10 - Linear Retrosynthetic Approach to N3-CTV



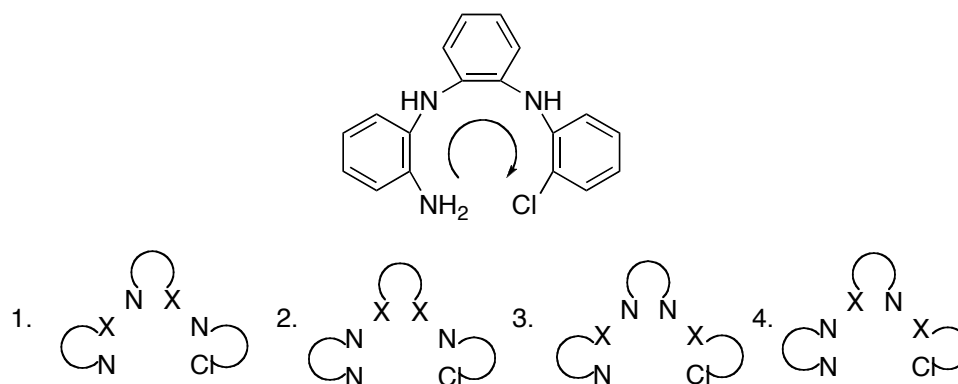
Although the linear retrosynthesis in Scheme 10 depicts a one-directional synthetic approach, there are two directional approaches in which the N3-CTV can be synthesized. The first strategy is to begin with the chlorine and build towards the terminal aniline (Scheme 11). There are four different ways in which this can be accomplished. The first o-substituted benzene contains the chloro group, which will be utilized in the final Buchwald-Hartwig closure, and either another halogen or a nitrogen containing substituent to enable coupling with the second ring. The second aromatic ring may be coupled to the first again with the complementary halogen and nitrogen substituent as required for Pd-catalyzed N-arylation. The final ring is incorporated in a similar fashion. Scheme 11 outlines the four different sequences that can be utilized in order to build the desired N3-CTV linearly beginning with a chlorine and ending with the aniline.

SCHEME 11 - Four Possible Synthetic Strategies Beginning With Chlorine and Building Towards the Aniline



Similarly, one can begin with the nitrogen required for the aniline and build to the triaryl precursor towards the chlorine to be used in the final N-arylation closing the 9-membered cyclophane (Scheme 12). Although both synthetic routes are very similar, there are many possibilities with respect to leaving group and nucleophilic nitrogen that can be utilized to form each C-N bond.

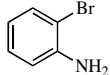

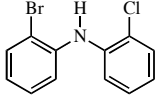
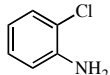

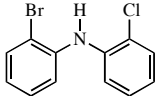
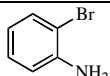

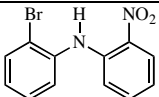
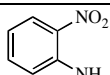

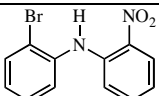
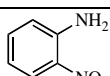

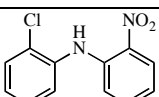
SCHEME 12 - Four Possible Synthetic Strategies Beginning With Aniline and Building Towards the Chlorine



Regardless of the direction we choose, the first step of the linear synthesis employs Buchwald-Hartwig Pd-catalyzed N-arylation chemistry to form an ortho-substituted diphenylamine, **A**. Unlike the diphenylamine used in the [2x1] approach discussed in chapter 2, this molecule contains both a halogen and primary aniline enabling the third ring to be coupled at either end. In order to find the most efficient set of conditions, several analogues were synthesized (Table 5). This also allowed for numerous options for the synthesis of subsequent steps, namely the synthesis of triarylamine **B**. For example, different halogens have different rates of reaction under Pd

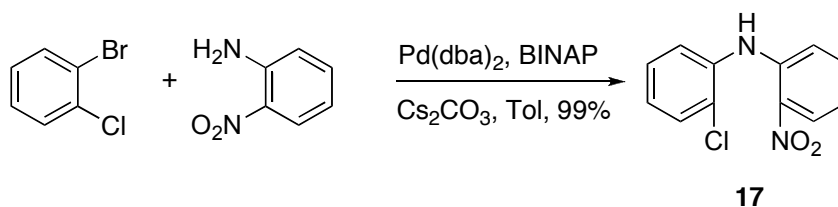
cross-coupling conditions; therefore utilizing two different halogens such as a chlorine and bromine (Table 5, entries 1 and 2) will make one end of the molecule more reactive, decreasing the probability of reaction occurring at both ends. Also, introducing an electron-withdrawing group such as a nitro group (Table 5, entries 3 and 4) precludes multiple reactive aniline nitrogens.

TABLE 5 - Synthesis of Diphenylamine Derivatives, Intermediate A

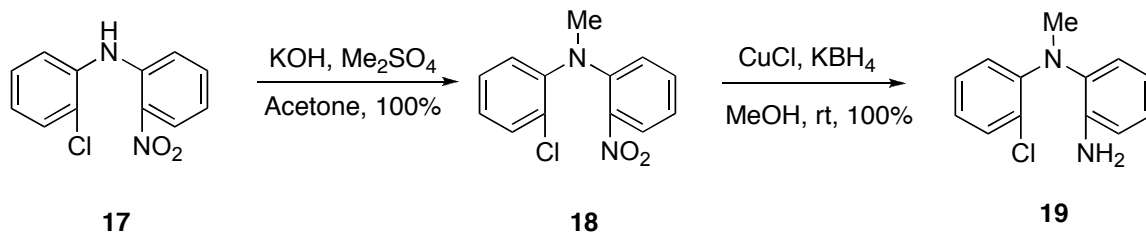
Aniline	Aryl Halide	Conditions	Product
		Pd(OAc) ₂ , DPEPhos, NaOtBu, tol	 27%
		Pd(OAc) ₂ , DPEPhos, NaOtBu, tol	 74-80%
		Pd(OAc) ₂ , BINAP, NaOtBu, p-xyl	 not isolated
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	 96%
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	 99%

The best set of conditions identified to afford intermediate **A** was a modification of the Buchwald-Hartwig N-arylation method used by Tietze *et al.*⁸⁶ Here, 1,2-bromochlorobenzene and o-nitroaniline were coupled employing Pd(dba)₂, BINAP and Cs₂CO₃ in dry toluene for 24 hours at 120°C. This gave 2-chloro-2'-nitrodiphenylamine **17** in 99% yield without further purification necessary (Scheme 13).

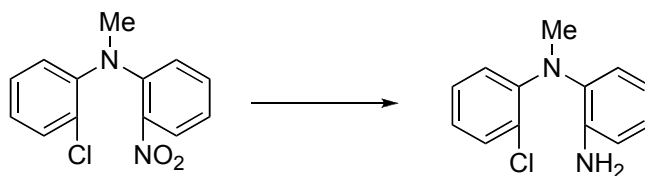
SCHEME 13 - Synthesis of Compound 17 (Intermediate A)



Protection of the aniline nitrogen was essential in order to eliminate unwanted phenazine-like by-products. The fairly acidic proton of the aniline could easily be abstracted by the base required for the cross-coupling reactions leaving the inappropriate nucleophile available for the 6-membered phenazine formation. The internal aniline was therefore protected by methylation using KOH and Me₂SO₄ in refluxing acetone according to the general procedure of Wilshire⁹² to give the N-methyl diphenylamine **18** in 100% yield with no need for purification. Compound **18** was easily reduced employing the general method of Sanz⁹³ using CuCl and KBH₄ in dry MeOH at room temperature to give **19** in 100% yield (Scheme 14).

SCHEME 14 - Methylation and Reduction of Intermediate A

More common reduction methods such as Pd/C and $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ or hydrogenation with H_2 and Pd/C gave dehalogenated and demethylated reduction products. For example, Pd/C and $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ gave a mixture of the dehalogenated and demethylated diphenylamine. Palladium can tightly bind chlorine and H_2NNH_2 can act as the nucleophile in an $\text{S}_{\text{N}}2$ attack displacing the methyl protecting group (Table 6, entry 1). When a dissolving metal reduction utilizing SnCl_2 and HCl in refluxing EtOH was employed, ^1H NMR data showed 95% conversion to the reduced aniline; however recovery was poor presumably due to the tight binding of the product with tin salts (Table 6, entry 2 and 3). Reduction via hydrogenation using RaNi and Pd/C under high pressure were also attempted, resulting only in the recovery of starting material (Table 6, entries 4, 5 and 7).

TABLE 6 - Attempted Reductions of Intermediate A

Entry	Conditions	Product
1	5% Pd/C, H ₂ NNH ₂ •H ₂ O, EtOH, reflux	 NH ₂
2	SnCl ₂ , HCl, EtOH, r.t.	 50% 50% recovered SM
3	SnCl ₂ , HCl, EtOH, reflux	 50% 95% conversion by ¹ HNMR, recovery, 53%
4	RaNi, H ₂ , EtOH, r.t. 1 atm	Recovered SM (95%)
5	10% Pd/C, H ₂ , EtOH, r.t. 1 atm	Recovered SM (95%)
6	Na ₂ S ₂ O ₄ , H ₂ O, THF	 42%
7	10% Pd/C, H ₂ , EtOH, r.t., 60 psi	 50% 50%

The next step in the linear synthesis was formation of the triarylamine derivative

B. The intention was to utilize the primary aniline of compound **19** as the point of attachment for the third aromatic ring employing either of two different reaction mechanisms. Formation of C-N bonds could be formed by Buchwald-Hartwig N-arylation, which had already proven to be successful. In addition, we hypothesized that a S_NAr reaction could also be utilized. Reaction conditions for S_NAr require an activated benzene ring with a good leaving group, base and a strong nucleophile. In this case, the nucleophile was the aniline and the activated ring was o-fluoronitrobenzene (Table 7, entry 6).

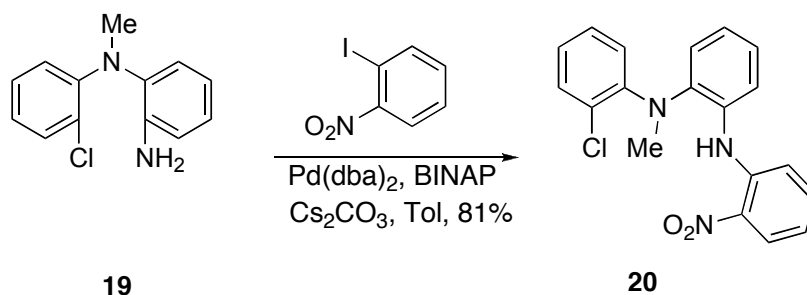
TABLE 7 - Synthetic Strategies for the Formation of Triarylamine **B**

Diphenyl amine	Substituted benzene	Conditions	Products
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	Multiple product spots
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	 18% 19% recovered SM
		Pd(dba) ₂ , DPEPhos, Cs ₂ CO ₃ , tol	 2% 1.7% 4.5% 20% recovered SM
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	 8%
		Pd(dba) ₂ , BINAP, Cs ₂ CO ₃ , tol	 81%
		DBU	 Recovered SM

As shown in Table 7, successful synthesis of the triarylamine **B** involved the methyl protected diphenylamine, **19**, which was coupled to o-iodonitrobenzene under Buchwald-Hartwig conditions utilizing Pd(dba)₂ as the catalyst, racemic BINAP as the

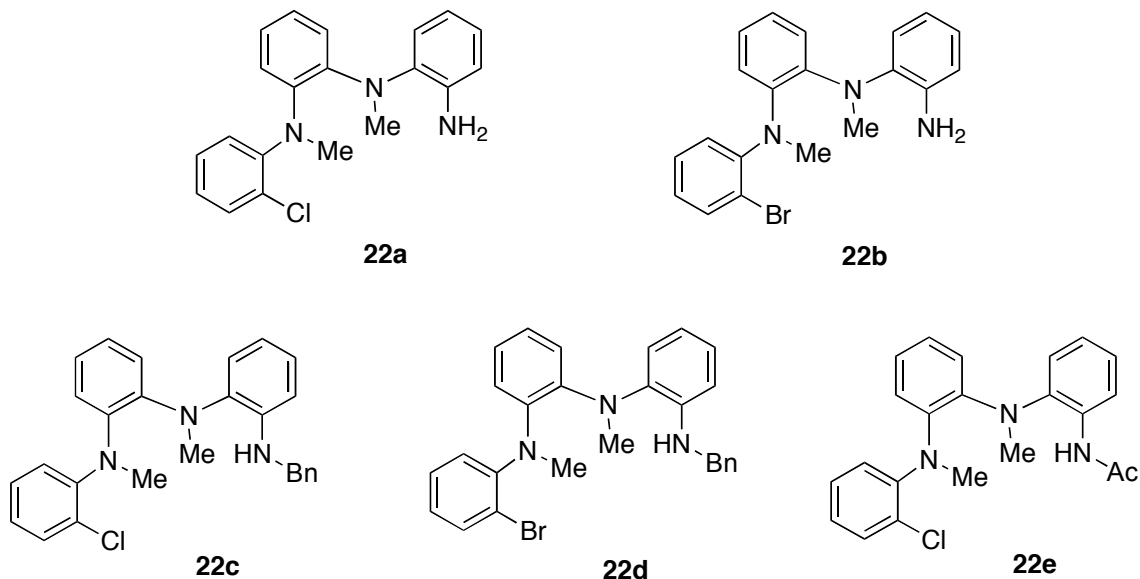
ligand, and Cs_2CO_3 as the base. The reaction was conducted under an argon atmosphere in a pressure tube at 120°C for 24 h. The resulting N,N'-diaryl-o-phenylenediamine **20** was synthesized in 81% yield following column chromatography (Scheme 15).

SCHEME 15 - Synthesis of Compound **20**, Triarylamine **B**

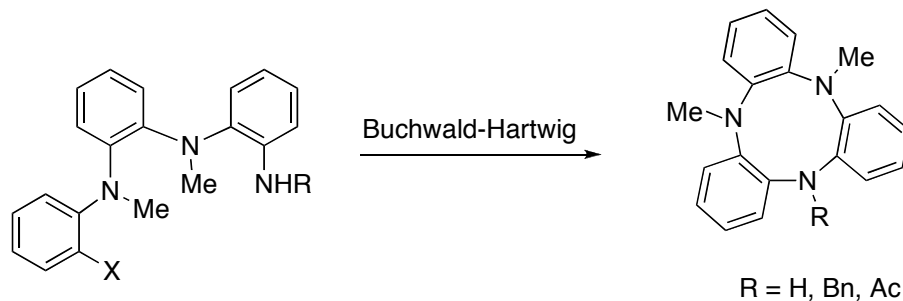


The formation of phenazine-like derivatives through the addition of the third benzene ring by Pd-catalyzed N-arylation (Table 7, entry 3) further solidified that the internal nitrogen was the point of nucleophilic attack for the 6-membered phenazine cyclization. Therefore, it seemed that protection of that internal nitrogen was critical in order to avoid unwanted phenazine-like by-products. Methylation was easily accomplished employing KH and MeI in DMF followed by reduction of the nitro group with CuCl and KBH_4 to give products **21** and **22a** respectively (Scheme 16).

With all the components of the desired triazacyclophane in place, we subjected compound **22a**, and several related derivatives (Figure 9) to Buchwald-Hartwig N-arylation conditions in order to afford the target N3-CTV scaffold which ultimately proved to be successful. Several analogues of the triarylamine **22a** were synthesized to be used in the attempted final closure to the 9-membered azacyclophane. Derivatives included two different halogens, bromine and chlorine each with different reactivities towards Pd-catalyzed N-arylation. Additionally, the terminal aniline was substituted with either a benzyl group or an acetyl group. The acetyl group lowered the pKa of the aniline proton thus making it more acidic. The benzyl group provided a secondary aniline providing only one reaction site. The benzyl and acetyl derivatives were successfully synthesized, **22c-e**, and subjected to a variety of Buchwald-Hartwig cross-coupling reactions along with compounds **22a** and **22b** (Figure 9, Table 8).

FIGURE 9 - Derivatives of Compound 22a

However, closure to the desired cyclophane was not easily attained and was highly dependent upon conditions. First, the final cyclization to the 9-membered cyclophane is an intramolecular reaction, therefore, the concentration of the overall reaction was kept dilute, (0.05-0.01M) in order to reduce the formation of oligomers by decreasing the rate at which molecules undergo intermolecular processes. Also, the key elements needed for the Buchwald-Hartwig N-arylation, namely catalyst and ligand, were used in very small quantities, (0.5-10% mol). The combination of small catalyst/ligand loading ratios with a very dilute solution made for conditions that failed to give rise to oxidative insertion of the Pd-phosphine complex into the haloaryl bond, let alone successfully undergo the N-arylation step (Table 8).

TABLE 8 - Attempted Final Cyclization Utilizing Buchwald-Hartwig Conditions

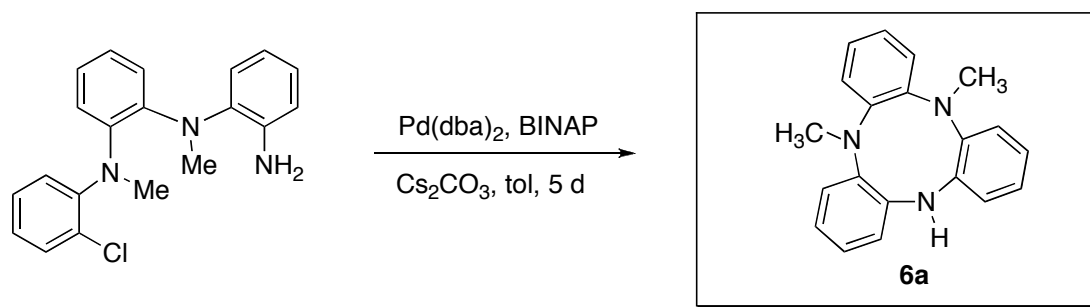
Derivative (22a-e)	Catalyst	Ligand	Base	Solvent	Time/Temp(°C)	Product
22a	(SIPr)Pd(Cin)Cl		KOtBu	DME	24 h / 75	SM
22a	(SIPr)Pd(Cin)Cl		KOtBu	DME	7 d / r.t.	Degradation of SM
22a	Pd(dba) ₂	P(tBu) ₃	Cs ₂ CO ₃	tol	7 d / r.t.	SM
22a	Pd(dba) ₂	P(tBu) ₃	Cs ₂ CO ₃	tol	5 d / 65	SM
22a	Pd(dba) ₂	P(tBu) ₃	KOtBu	tol	5 d / 65	SM
22a	Pd(OAc) ₂	P(tBu) ₃	KOtBu	tol	5 d / 65	SM
22a	Pd(OAc) ₂	P(tBu) ₃	Cs ₂ CO ₃	tol	5 d / 65	SM
22b	(SIPr)Pd(Cin)Cl		KOtBu	tol	5 d / 75	SM
22b	(SIPr)Pd(Cin)Cl		Cs ₂ CO ₃	tol	5 d / 75	SM
22c	Pd(dba) ₂	BINAP	Cs ₂ CO ₃	tol	32 h / 75-110	SM
22c	Pd(dba) ₂	P(tBu) ₃	NaOtBu	tol	7 d / r.t.	SM
22d	(SIPr)Pd(Cin)Cl		LiHMDS	DME	48 h / r.t. – 60	SM
22d	Pd(dba) ₂	BINAP	LiHMDS	tol	24 h / 110	SM
22d	Pd(dba) ₂	P(tBu) ₃	LiHMDS	tol	24 h / 110	SM
22d	Pd(OAc) ₂	P(tBu) ₃	LiHMDS	tol	24 h / 110	SM
22e	Pd(dba) ₂	BINAP	Cs ₂ CO ₃	tol	48 h / 110	SM

* (SIPr)Pd(Cin)Cl – Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2,6-di-i-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II)

In a similar reaction, derivative **22a** was treated with the following Buchwald-Hartwig conditions: Pd(dba)₂, BINAP, Cs₂CO₃ in toluene at 130°C in a sealed tube. After 24 h, no reaction took place based on TLC analysis. The reaction mixture was recharged with another loading of catalyst and ligand and allowed to stir for another 24 h in a 130°C oil bath. The reaction was removed from the oil bath and TLC showed no

reaction. Once more the mixture was recharged with catalyst and ligand and allowed to react for another 48 h, upon which TLC showed 2 new spots. After purification by column chromatography, we were able to isolate the desired N,N'-dimethyl N3-CTV derivative **6a** in 5% yield.

FIGURE 10 – N,N'-Dimethyl N3-CTV

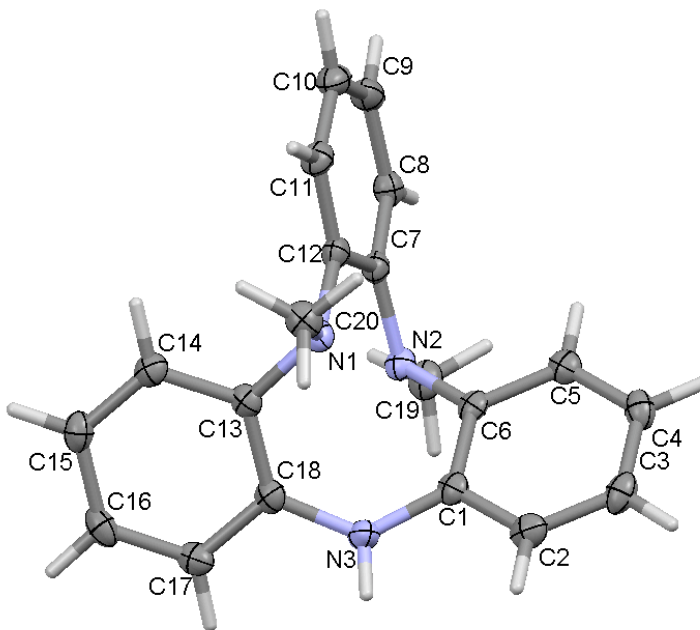


The continual recharging of the reaction mixture with catalyst and ligand increased the concentration of the catalyst/ligand complex finally enabling insertion into the haloaryl bond.

The structure of N,N'-dimethyl N3-CTV was confirmed by multiple characterization methods. In the ¹H NMR, methyl groups are observed at δ 2.68 (6H, s), and the NH observed at δ 5.82 (1H, bs). ¹³C NMR confirms the presence of 10 different carbons, six tertiary and three quaternary in the aromatic region, as well as one aliphatic carbon at δ 39.9 ppm. The calculated mass of MH⁺ for the N,N'-dimethyl N3-CTV is 302.1657; TOFMS shows a M+1 at 302.1573. Finally, single crystal X-ray analysis confirmed the structure and shows that the N3-CTV molecule adopts a C₂-symmetric

saddle conformation, unlike the parent CTV which exists almost exclusively in the crown-conformation (Figure 11).

FIGURE 11 - X-ray Structure of N,N'-Dimethyl N3-CTV with Atom Labels, Thermal Ellipsoids are at the 50% Probability Level.



Although the target molecule was successfully isolated as the N,N'-dimethyl derivative **6a**, the reaction conditions were not ideal and the yield was low (5%). Multiple catalyst loadings and long reaction times led to a very poor conversion to the desired N3-CTV derivative. One way we were able to improve the yield of the final cyclization step was by employing the use of a microwave reactor for the Buchwald-Hartwig cross-coupling reaction. Microwave-assisted organic synthesis is a rapidly growing practice.⁹⁴⁻⁹⁷ Microwave (MW) reactors enable shorter reaction times, better

conversion and lower catalytic loading ratios. Microwaves allow for irradiation to be very localized as opposed to thermal heating, which is widely dispersed.

In addition to microwave irradiation, the catalyst and ligand were increased to a stoichiometric amount rather than the typical 0.5-10% catalytic loading ratios generally employed. The final reaction step was conducted in a CEM Discover[®] Microwave, using Pd(dba)₂, BINAP, Cs₂CO₃ in toluene with a reaction concentration of 0.1 M. The MW conditions employed for the final cyclization were as follows: temperature of 150°C, 200 psi, 240 min. With these changes, the overall isolated yield of the final cyclization step increased to 50% versus the initial 5% isolated after multiple catalyst/ligand loadings and under thermal heating conditions. To compare whether MW irradiation was better than thermal heating, another experiment was conducted with a stoichiometric amount of catalyst and ligand under thermal heating. After a reaction period of 5 days at 120°C, 10 mg of the desired N,N'-dimethyl N3-CTV was isolated after purification by column chromatography, representing 20% of the theoretical yield. Based on these results, it is clear the MW heating is more efficient than thermal heating in the closure of the 9-membered N3-CTV.

Conditions for the final step in the synthesis have not yet been completely optimized. Several different factors can cause a microwave tube to explode, leading to loss of material. For example, the choice of solvent is important because of solubility. If the palladium-ligand complex is not soluble in a particular solvent, then the palladium will precipitate out of solution and form a mirror on the inside of the tube; this mirror causes

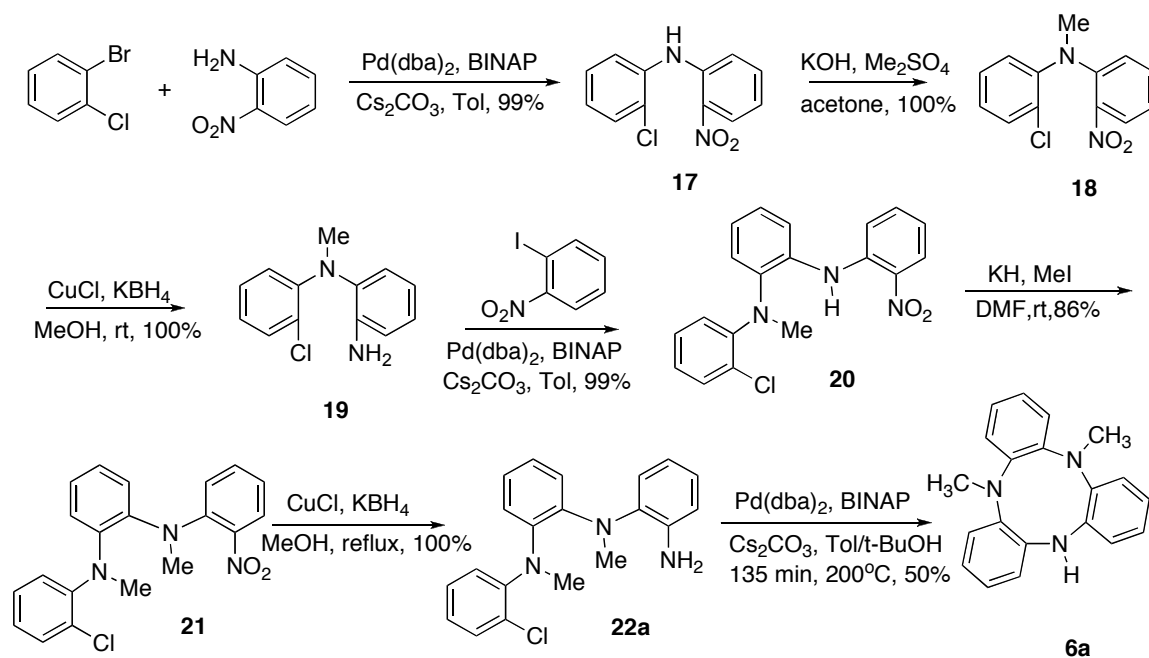
the tube to burst upon MW heating. Similarly, increasing the concentration of the overall reaction by decreasing the total amount of solvent leads to bursting of the MW tube.

Presumably, this occurs because using a stoichiometric quantity of Pd-complex in a smaller amount of solvent leads to insufficient solubility of the catalyst-ligand complex. Ideal reaction conditions would allow for a catalytic loading ratio of the palladium-ligand complex along with a more concentrated overall reaction solution. Currently, the MW reactor in our lab only allows for a minimum of 1 mL of solvent in a 10 mL vessel; efforts are focused on finding ways to utilize the MW for smaller microscale synthesis.

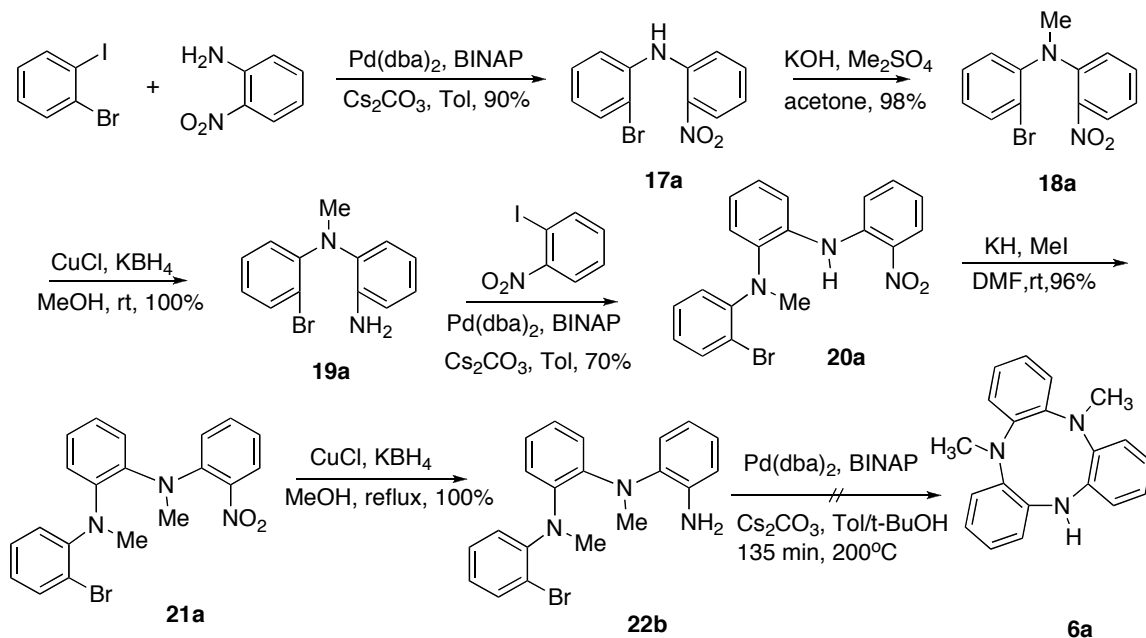
Scheme 17 summarizes the complete synthesis of N,N'-dimethyl N3-CTV in 42% overall yield. A modification of the Buchwald-Hartwig N-arylation method used by Tietze *et al.*⁸⁶ of 1,2-bromochlorobenzene and o-nitroaniline gives 2-chloro-2'-nitrodiphenylamine **17** in 99% yield. The amine was protected by methylation using KOH and Me₂SO₄ in refluxing acetone⁹² to giving the N-methyl diphenylamine **18** in quantitative yield. Compound **18** was easily reduced employing the general method of Sanz⁹³ using CuCl and KBH₄ in dry MeOH at room temperature to give **19** in 100% yield. The aniline **19** was coupled to iodonitrobenzene through the previously established Buchwald-Hartwig conditions to produce the triaryl amine **20** in 99% yield. Compound **20** was subjected to methylation by KH and MeI followed by reduction of the nitro group with CuCl and KBH₄ to give products **21** and **22a**, respectively. The triaryl aniline was successfully closed to the 9-membered cyclophane through the use of Buchwald-Hartwig coupling in a microwave reactor to afford the desired dimethyl N3-CTV **6a** in

50% isolated yield.

SCHEME 17 - Complete Linear Synthesis of N,N'-Dimethyl N3-CTV



The same overall synthesis was completed replacing the chlorine atom with bromine (Scheme 18). It was thought that the bromine derivative would be more reactive towards Buchwald-Hartwig N-arylation in the final cyclization step. Attempted closures with bromine under thermal heating were unsuccessful in producing the desired N3-CTV. The final cyclization of the bromo triaryl derivative **22b** to the triazacyclophane using higher catalyst/ligand concentrations and MW irradiation that were successful for the chloro derivative have not yet been employed.

SCHEME 18 - Attempted Synthesis of N3-CTV with Bromine Substituent

In conclusion, we have shown that the synthesis of the ortho-cyclophane, N,N'-dimethyl N3-CTV can be achieved in 7 steps in 42% overall yield. Palladium catalyzed N-arylation, followed by alkylation and reduction was reiterated in order to obtain the triaryl precursor to the final palladium-catalyzed cyclization to the 9-membered cyclophane. The new N3-CTV cyclophane scaffold complements the familiar carbocyclic CTV framework as discussed previously.

CHAPTER 4

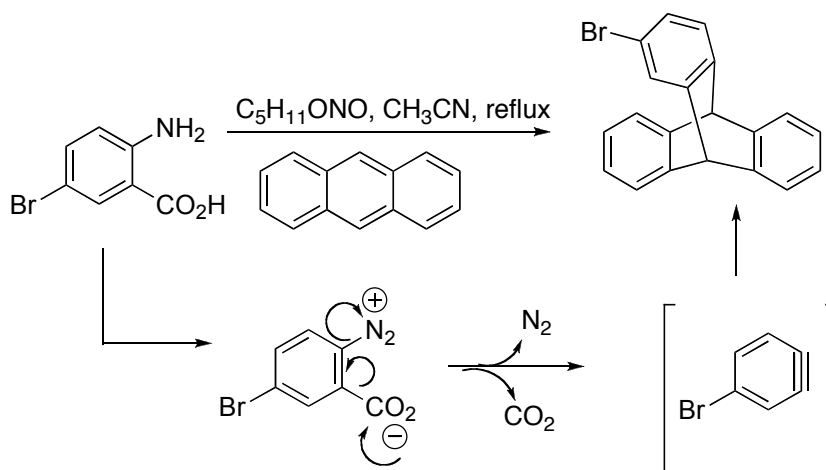
BENZYNE CLOSURE

In addition to the Buchwald-Hartwig Pd-catalyzed N-arylation, the final closure to the 9-membered ring of N3-CTV was attempted by employing a highly reactive benzyne intermediate. Benzyne chemistry and its application to organic synthesis has been recently reviewed by Sanz.⁹⁸ A benzyne intermediate is better described as a strained alkyne that is significantly weaker than its linear counterpart. Arynes are very reactive, even at low temperatures, and therefore must be generated *in situ*. Benzyne intermediates have low-lying LUMO's making them highly reactive species. The aryne intermediate can react in a variety of cycloadditions and *ene* reactions with alkenes. Another effect of the low-lying LUMO is that arynes behave as a powerful electrophiles.

A benzyne intermediate can be generated from a variety of methods such as via aryl anions, zwitterions and aryl radicals. A route that is often utilized in the formation of a benzyne intermediate is the elimination of a leaving group in the ortho-position of a metallated aromatic ring.⁹⁸ Aryl anions can also be generated from o-metallation of aromatic halides^{99, 100} and triflates¹⁰¹ with strong bases. Additionally, a benzyne

intermediate may be generated from an aryl radical. For example irradiation of 1,2-diiodobenzene has been shown to lead to benzyne derived products.¹⁰² Lastly, the zwitterions derived from anthranilic acids have been employed to produce arynes. Anthranilic acids are readily diazotated when mixed with an alkyl nitrile in an aprotic solvent leading to the formation of a benzenediazonium-2-carboxylate. Subsequent loss of N_2 and CO_2 lead to the aryne intermediate (Scheme 19).¹⁰³ The anthranilic acid is noteworthy in preserving an aryl bromide through the reaction.

SCHEME 19 - Formation of a Benzyne Intermediate Through a Zwitterion

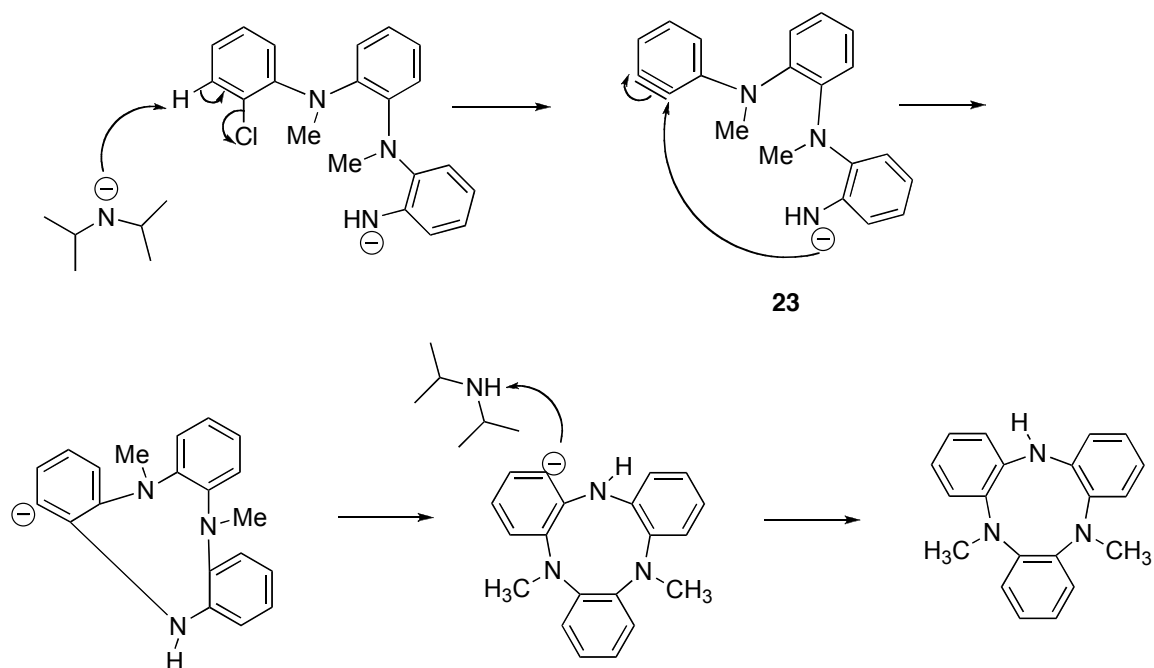


Arynes undergo many different reactions, making them extremely useful in organic synthesis. Some examples include pericyclic reactions e.g. benzyne intermediates readily undergo Diels-Alder cycloadditions with *cis* dienes such as furan. Similarly, arynes can participate in [2+2] cycloadditions with alkenes and carbon-heteroatom double bonds as well as [3+2] cycloadditions with stable 1,3-dipolar compounds.

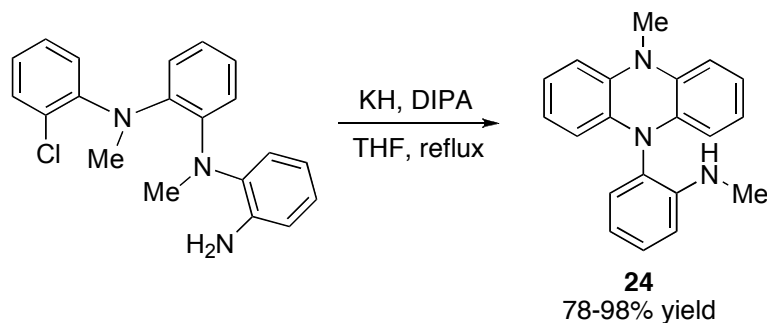
Nucleophilic addition to arynes has been widely used in the synthesis of complex organic molecules. Even neutral nucleophiles will readily add to a benzyne intermediate.^{98,104,105} Benzyne cyclization,^{106,107} in which the nucleophile is a substituent attached to the aryne intermediate is a simple way to construct benzo-fused carbocycles and heterocycles.⁹⁸ Biehl and coworkers have shown the preparation of five and six-membered heterocycles by nucleophilic addition to arynes and have also suggested the importance of nucleophilic addition to arynes in the synthesis of seven and eight membered rings that contain heteroatoms, including sulfur and nitrogen.¹⁰⁸ Futher, Larock showed how N-arylation could be accomplished without transition metals by enabling amines, sulfonamides and other substrates to react with arynes generated from o-silylaryl triflates.¹⁰⁹⁻¹¹¹

The proposed mechanism for the benzyne cyclization to the 9-membered N,N'-dimethyl N3-CTV derivative is shown in Scheme 20. A strong base abstracts a relatively acidic aniline proton, then abstracts a proton ortho to the halogen leaving group generating the aryne intermediate **23**. The aryne may then be attacked by the nitrogen nucleophile of the terminal aniline. Molecular models have shown that the orbital overlap is ideal for the formation of the desired 9-membered cyclophane.

SCHEME 20 - Proposed Mechanism of the Benzyne Cyclization

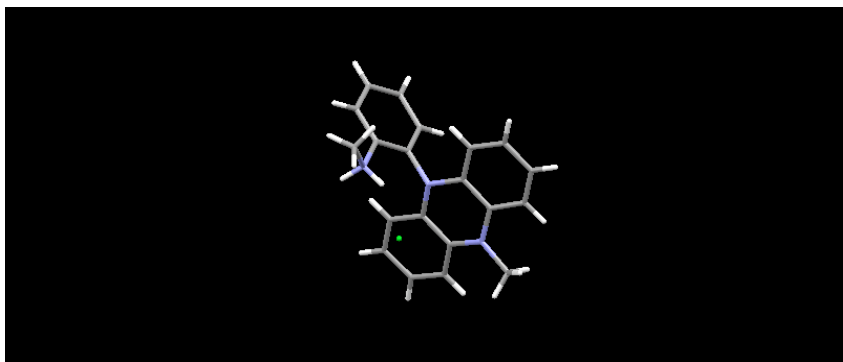


In the attempted closure via a benzyne intermediate to the 9-membered cyclophane employing KDA as the base, in refluxing THF, a methyl shift was observed producing a 6-membered phenazine derivative **24** instead of the desired triaza N3-CTV derivative (Scheme 21).

SCHEME 21 - Formation of the Methyl-Shifted Phenazine Derivative

Preliminary data was encouraging, as MS data showed an MH^+ of 302 suggesting that the N3-CTV had indeed formed. The 1H NMR data indicated an unsymmetrical molecule with 7 unique aromatic hydrogens rather than the six protons that one would expect for the N3-CTV target from the molecule's high 3_{cv} symmetry. Also, there were two different methyl peaks present in the 1H NMR. In the target N3-CTV both methyl protecting groups are equivalent, therefore further characterization was needed. Crystals of the HCl salt were formed from DCM/Hex and the identity of the methyl-shifted phenazine derivative was confirmed by single crystal X-ray analysis (Figure 12).

FIGURE 12 – X-Ray Crystal Structure of the Methyl-Shifted Phenazine Derivative HCl Salt

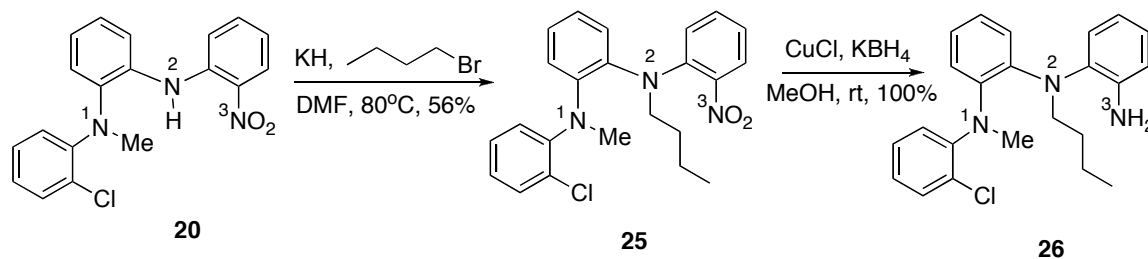


The phenazine by-product was unexpected since molecular models predicted a clean overlap of orbitals to form the 9-membered ring, yet the reaction proceeds exceptionally well, with only the phenazine derivative as the major product formed and isolated, with no further purification required. It is hypothesized that the methyl shift proceeds either through an intermolecular or intramolecular S_N2 dealkylation. Table 9 outlines the different reaction conditions utilized in the attempted benzyne closure. Halobenzenes are generally unreactive, requiring the use of a very strong base. Since alkyllithium reagents are known to participate in lithium-halogen exchange which precludes the formation of the benzyne intermediate,¹¹² KDA was employed as the base for all of the benzyne reactions. KDA was generated in situ with KH and N,N'-diisopropylamine (DIPA) in THF, followed by addition of the triarylamine substrate. In all trials the base and solvent were kept constant while the halogen leaving group and temperature were varied. The mechanism by which the methyl shift occurs appears to be

dependent on both the halogen present and the alkyl group protecting the internal nitrogen.

When the reaction was conducted between -78°C to rt (Table 9, entry 1) the result was a 96% recovery of starting material. The reaction mixture was then heated to reflux, (Table 9, entry 2) and the methyl shift was observed, resulting in the 6-membered phenazine derivative **24**. Thus the benzyne intermediate had formed and the alkyl shift had occurred. We did not know whether the benzyne formation or the alkyl shift occurred first. Our initial assumption was that the benzyne would react with the less hindered and more nucleophilic deprotonated terminal aniline rather than the methyl-protected internal aniline. In an attempt to slow the rate of the $\text{S}_{\text{N}}2$ reaction, with the assumption that demethylation preceded and was essential for phenazine formation, the incorporation of a more sterically hindered protecting group on the internal nitrogen was considered. Most attempts at incorporating a bulkier protecting group proved to be unsuccessful with the exception of n-butyl bromide that was added to compound **20** in 56% yield with KH in DMF at 80°C over 2 hours to give N-methyl-N'-butyl triaryl derivative **25**. The n-butyl derivative, **25**, was reduced to the triaryl n-butylamine **26** employing CuCl , KBH_4 , in dry MeOH to give the aniline in quantitative yield (Scheme 22).

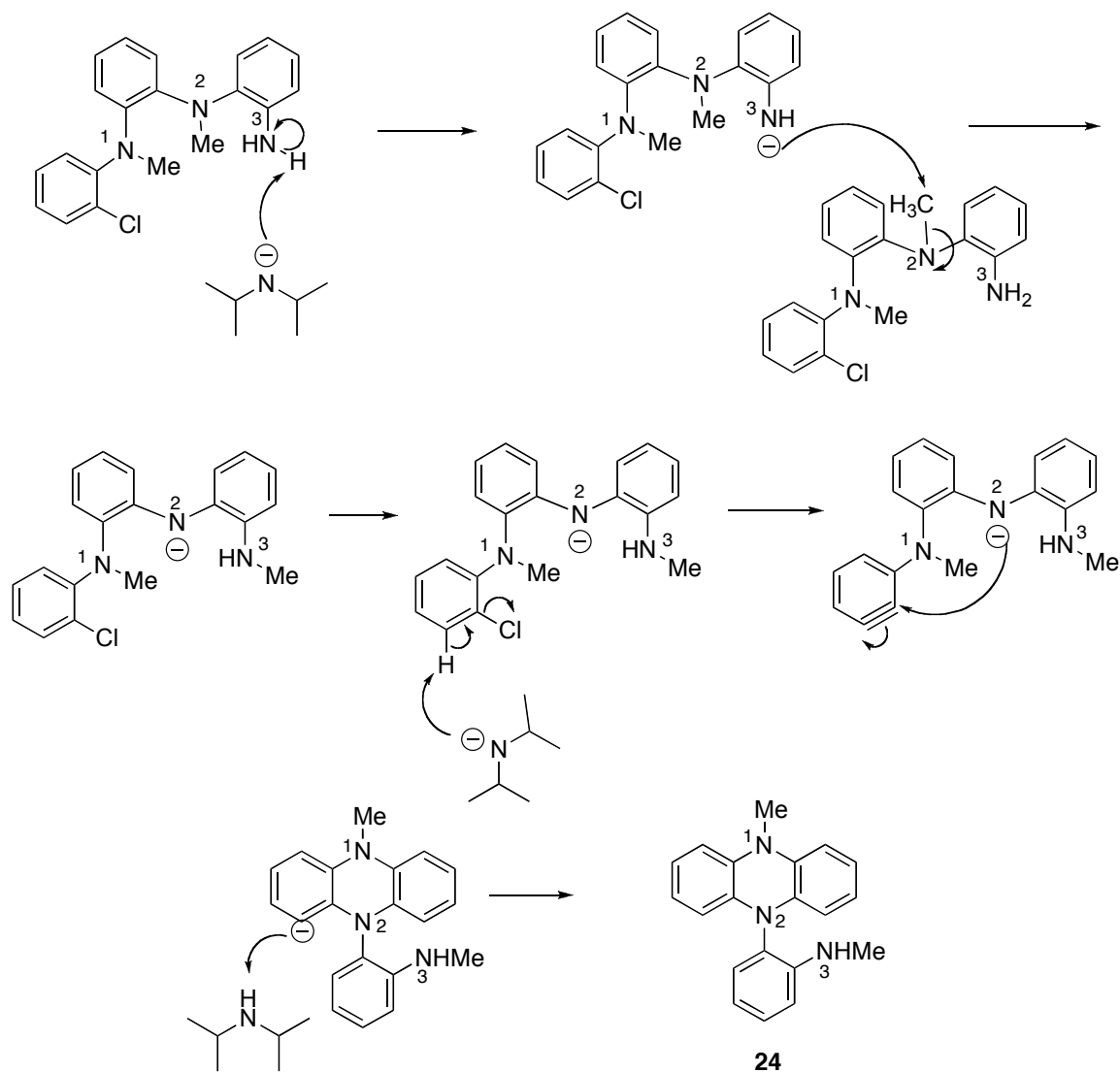
SCHEME 22 - Protection of the Internal Nitrogen with n-Butyl Bromide



When the triaryl n-butyl derivative **26** was subjected to the same set of benzyne conditions (KH, DIPA, THF, reflux), the alkyl shift was not observed and only starting material was recovered (Table 9, entry 3) which suggests that the benzyne formation is somehow dependent upon prior alkyl shift since the N,N'-dimethyl derivative *did* afford the methyl-shifted phenazine under the same conditions. Alkyl transfer of the butyl group was seen only when the reaction was conducted in a sealed pressure vessel at 95°C (Table 9, entry 4) with concomitant formation of the phenazine derivative **24**. The temperature difference between the methyl and butyl shift are consistent with a 50-fold difference in the rate of reaction for a methyl versus primary alkane in an S_N2 type reaction.¹¹³ Based on these results, it is hypothesized that the rate of dealkylation in the case of R = Me is faster than the rate of the benzyne formation indicating the following sequence of events: first, the terminal aniline is deprotonated followed by intermolecular or intramolecular dealkylation. Then the benzyne intermediate is formed enabling the closure to the 6-membered phenazine derivative (Scheme 23). The terminal aniline nitrogen, N3 is more basic, therefore the equilibrium would be to the right towards N2, but this begs the question of why N1 is not dealkylated? The relative pK_a of N1~N2; which suggests the possibility of either a dynamic equilibrium between N1 and N2 which is not satisfying

since the phenazine is N1-CH₃ and not a mixture of N1-CH₃ and N1-H. This suggests the possibility of an intramolecular transfer.

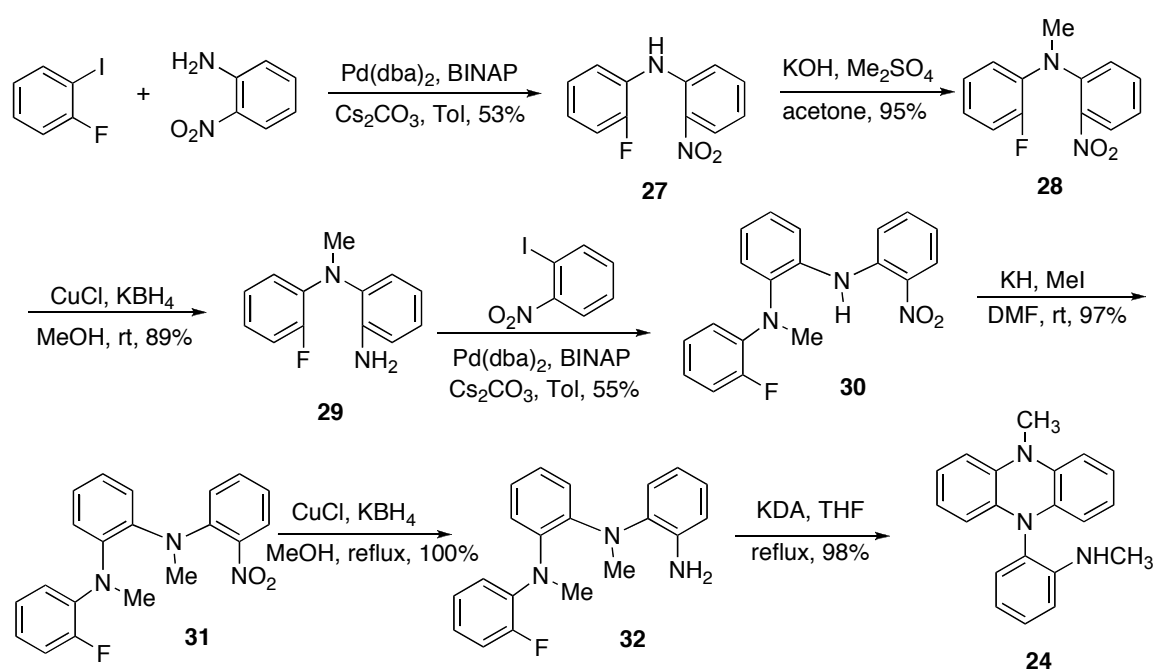
SCHEME 23 - Proposed Mechanism for the Formation of the 6-membered Phenazine Derivative From N,N'-Dimethyl Derivative



We were encouraged by the lack of alkyl shift with R = Bu and reasoned that if the benzyne could be formed under milder conditions then N₂ would remain protected by the n-butyl group and circumvent 6-membered ring formation. We therefore decided to change the halogen from chlorine to fluorine. Rao and coworkers suggested that the more electronegative the halogen used as a leaving group in the formation of a benzyne intermediate, the better it will stabilize the negative charge placed on the adjacent carbon.¹¹² Thus employing a fluorine atom as a leaving group will form the benzyne intermediate faster than using a chlorine or bromine. Therefore, we substituted the chlorine atom with a fluorine (Table 9, entry 5) by employing the same 6-step linear synthesis, beginning with o-fluoroiodobenzene and o-nitroaniline in a Buchwald-Hartwig N-arylation to give 2-fluoro-2'-nitrodiphenylamine **27** in 53% yield after purification by column chromatography (Scheme 24). The synthesis was carried out in exactly the same way as it was for the chlorine and bromine in chapter 3. The amine was protected by methylation using KOH and Me₂SO₄ in refluxing acetone⁹² to give the N-methyl diphenylamine **28** in 95% yield. Compound **28** was easily reduced employing the general method of Sanz⁹³ using CuCl and KBH₄ in dry MeOH at room temperature to give **29** in 89% yield. The aniline **29** was coupled to iodonitrobenzene through the previously established Buchwald-Hartwig conditions to produce the triaryl amine **30** in 55% yield after purification by column chromatography. Compound **30** was subjected to methylation by KH and MeI followed by reduction of the nitro group with CuCl and KBH₄ to give products **31** and **32** respectively. When the fluoro triaryl derivative **32** was subjected to benzyne conditions, KDA in refluxing THF, the resulting product was the

phenazine derivative in 98% isolated yield. The overall yields of the Buchwald-Hartwig couplings are lower than those for the chlorine and bromine derivatives, but they are clean reactions and the remaining mass balance is recovered SM for both coupling reactions.

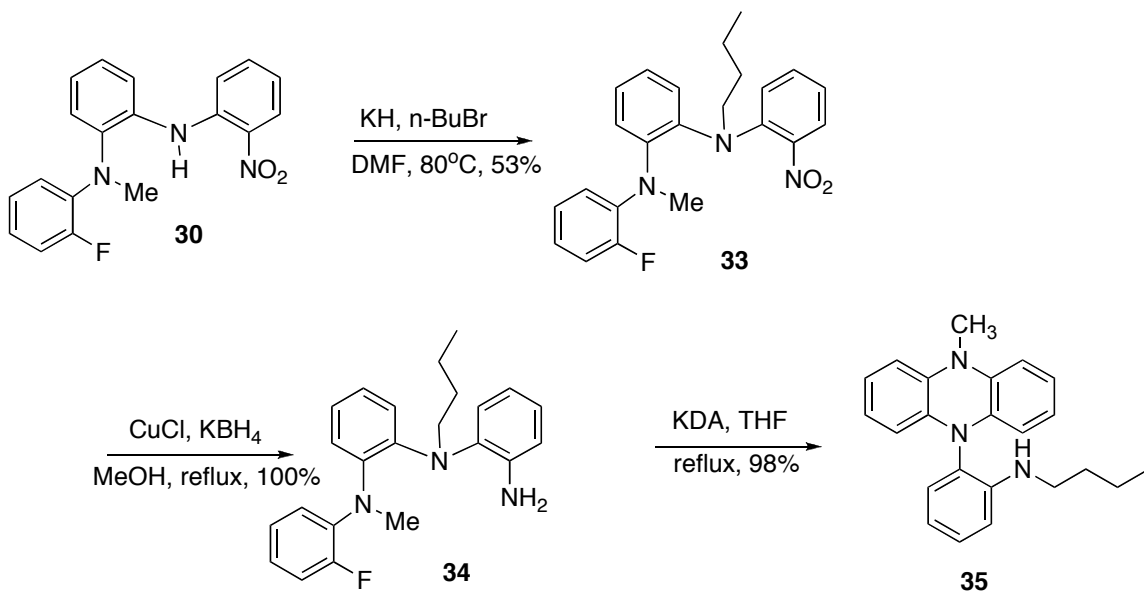
SCHEME 24 - Linear Synthesis of the Fluorinated Triarylamine **32**



The formation of phenazine derivative **24** with a fluorine halogen led us to introduce an n-butyl protecting group on N2 as was done previously with compound **25**. The n-butyl protecting group was added to the fluoro triarylamine, **30**, using KH and n-butyl bromide in DMF at 80°C followed by reduction of the nitro group with CuCl and KBH₄ in MeOH to give compounds **33** and **34** respectively. When the triarylamine

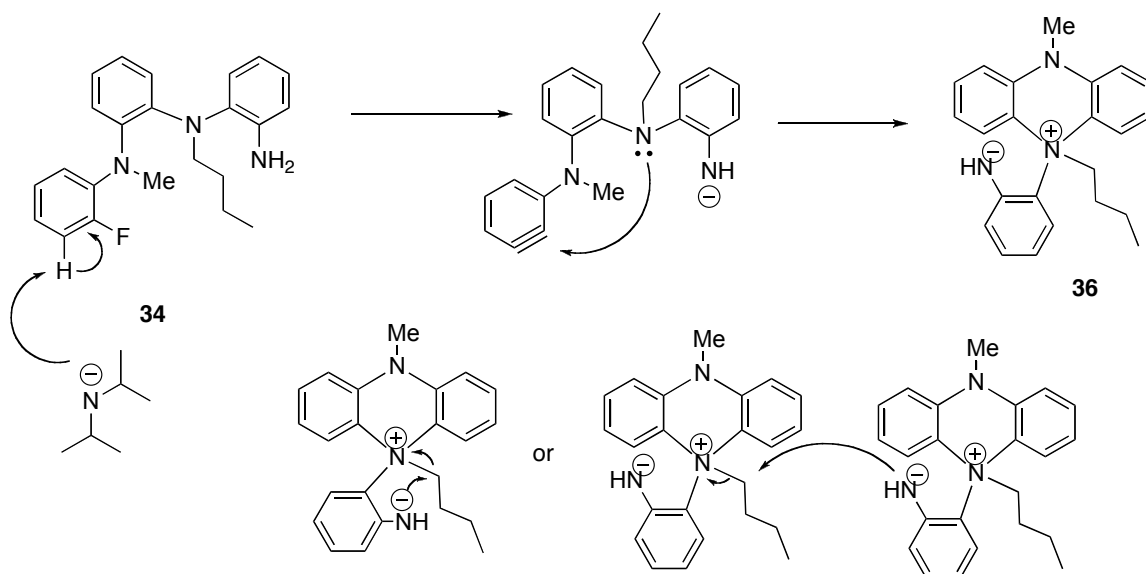
containing the fluorine and the n-butyl protecting group **34** was subjected to benzyne conditions, KDA in refluxing THF, the alkyl transfer was once again observed giving rise to phenazine **35** in 98% isolated yield, thus suggesting that the formation of the benzyne intermediate precedes that of the alkyl transfer (Scheme 25).

SCHEME 25 – Synthesis of Compound **34** Fluoro-N-Methyl-N'-Butyl Substrate



The change in the reaction sequence and the isolation of **35** suggests the intermediary of a very interesting zwitterion, **36**, which appears to be formed from a neutral, tertiary amine attacking the benzyne intermediate, followed by an intra- or intermolecular $\text{S}_{\text{N}}2$ dealkylation (Scheme 26).

SCHEME 26 - Proposed Mechanism for the Formation of the Butyl-Shifted Phenazine Derivative

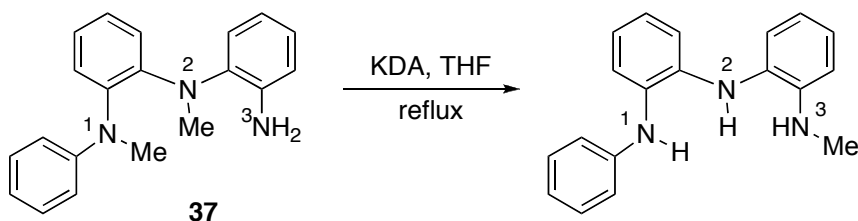


The formation of zwitterion **36** via attack on a benzyne by a tertiary, neutral aniline is not without precedent. A similar result was reported by Kunai and co-workers¹¹⁴ wherein a nucleophilic nitrogen atom of an imidazole adds to an aryne, forming a zwitterion which becomes the neutral product after abstraction of a proton, consistent with our proposed mechanism. Since the internal nitrogen (N2) of the triarylamine has no proton to abstract, dealkylation is required to lead to the neutral phenazine derivative.

In order to determine if dealkylation is dependent on prior benzyne formation, the reaction was conducted under the same conditions without a halogen leaving group present. Two different triarylamine derivatives were synthesized without a leaving group. The first triarylamine derivative contained methyl groups on both nitrogens **37**, while another triarylamine derivative contained a methyl group and an n-butyl protecting group **38**. When compound **37** was subjected to KDA in refluxing THF, double demethylation was

observed in addition to a methyl group present on the terminal aniline (Scheme 27). This result suggests dealkylation can occur independent of benzyne formation, at least when the N-substituent is a methyl group. It is surprising that both methyls were removed given that in previous reactions the methyl-protecting group on N1 remained in place. This shows that the diisopropylamide base may function as the nucleophile in demethylation. Furthermore, it demonstrates that demethylation is slower than phenazine formation and that once the phenazine forms, the phenazine N-methyl at the 2-position does not undergo dealkylation. This also suggests that the lability of the N1-methyl group is precluded by prior formation of the phenazine, i.e. the N1-methyl group is more resistant to dealkylation after formation of the phenazine, as expected from our initial theory. Thus, N1-dealkylation is slower than phenazine formation.

SCHEME 27 - Intermolecular Double-Demethylation



When aniline **38**, containing both N1-methyl and N2-butyl groups but no halogen was subjected to KDA in THF at reflux, the observed product only showed alkyl shift of the N1-methyl group to the terminal aniline. The n-butyl group remained on the nitrogen in the N2 position, as observed by ^1H NMR. This result indicates that at least one demethylation occurs through an intermolecular process and that the methyl shift from

the nitrogen in the 1 position to the terminal aniline nitrogen in the 3 position need not be transferred directly, which is unlikely given the angle of attack is not ideal for an S_N2 reaction for the proximal N2-methyl. In addition, alkyl shift of the n-butyl protecting group may be dependent on the formation of the benzyne intermediate as noted above. Therefore, the non-halo experiment demonstrates that the alkyl shift can occur without benzyne formation and indicates a difference in reaction sequences dependent upon the halogen present and the N2-protecting group.

SCHEME 28 - Attempted Dealkylation of Butyl Protecting Group in the Absence of a Halogen

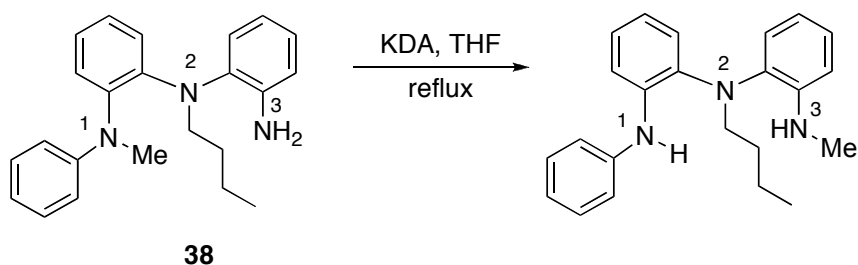
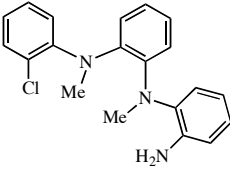
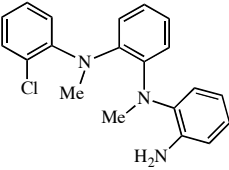
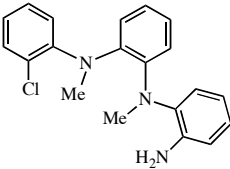
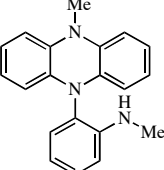
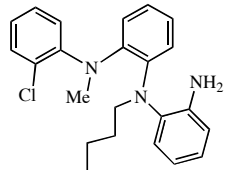
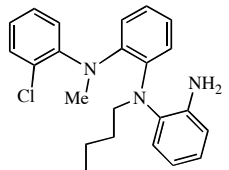
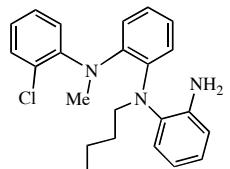
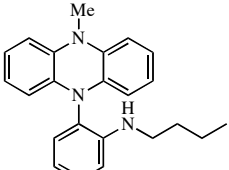
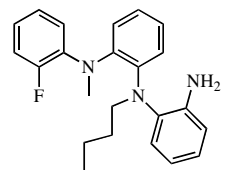
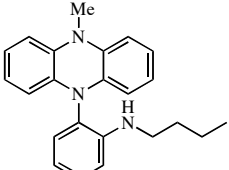


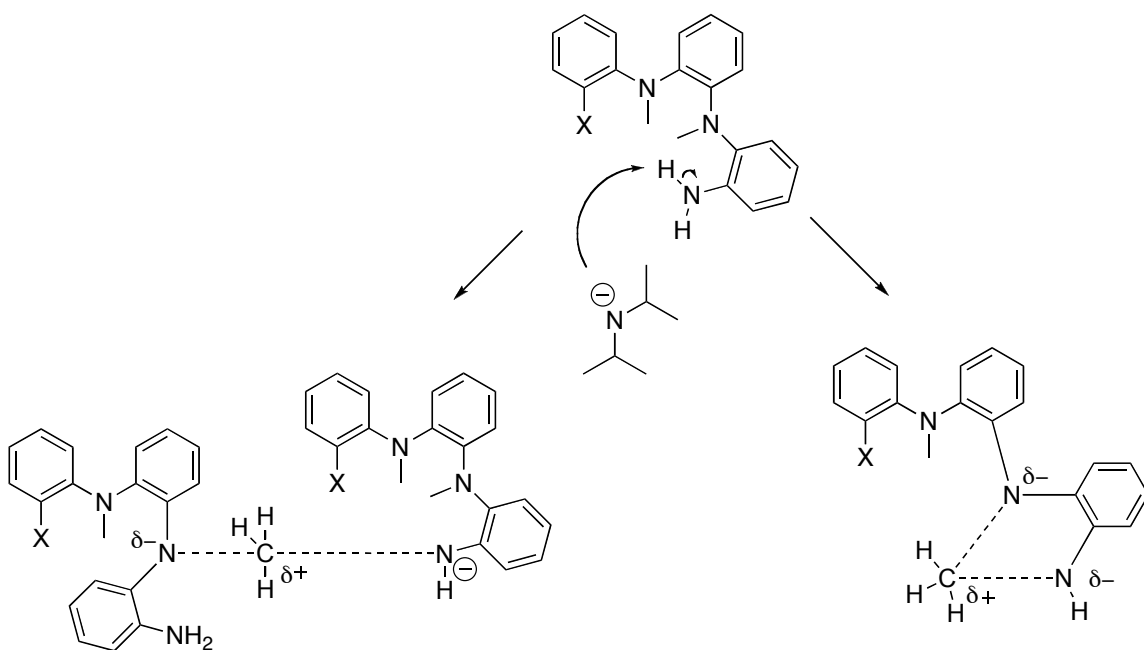
TABLE 9 - Attempted Benzyne Cyclization to N3-CTV

Entry	Starting material	Temp.	Product formed
1		-78°C to r.t.	 96% recovered SM
2		r.t. to 66°C	 78-98%
3		r.t. to 66°C	 96% recovered SM
4		r.t. to 95°C	 63%
5		r.t. to 66°C	 87%

It is unclear whether the S_N2 attack on the alkyl group occurs intra- or intermolecularly.

One argument against an intramolecular S_N2 dealkylation is that the angle of attack is not linear, whereas a linear, back-side attack is possible for an intermolecular reaction (Scheme 29).

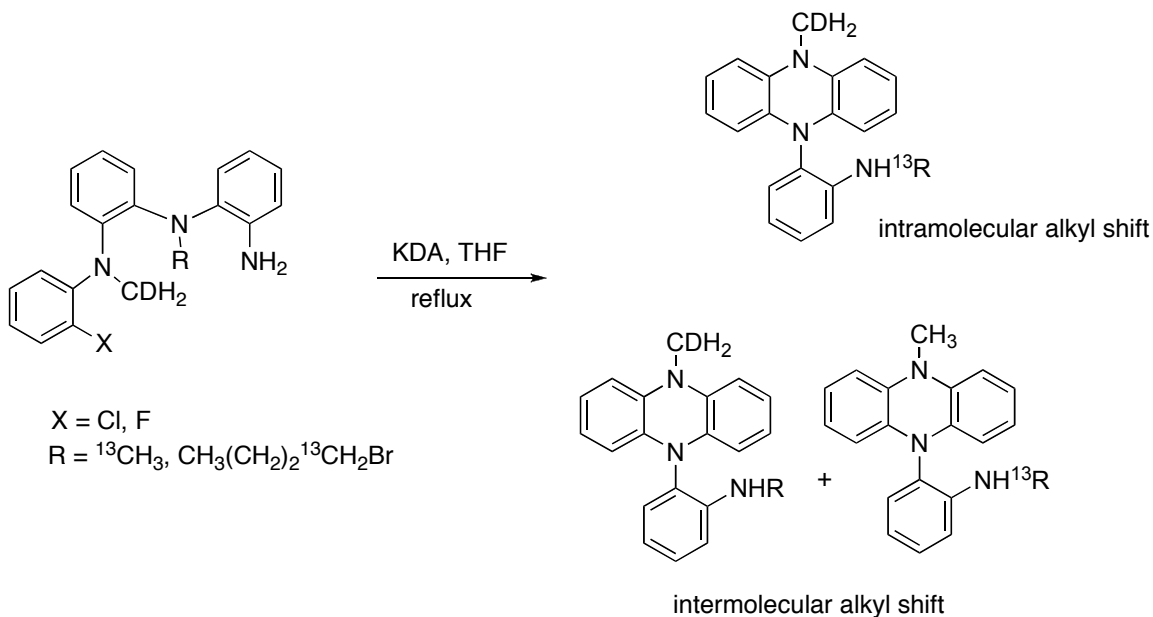
SCHEME 29 - Intermolecular vs. Intramolecular Dealkylation



Possible future experiments include labeling studies that should enable us to determine whether the dealkylation is occurring intra- or intermolecularly. For example, each protective N -alkyl group could be labeled with either deuterium or ^{13}C on the same triarylamine. This labeled compound would be mixed with unlabeled starting material and the mixture would be subjected to the benzyne conditions in the same reaction. If

both labels remain on the same phenazine derivative, then the alkyl shift is taking place by an intramolecular alkyl transfer. If labeled alkyl groups end up on different phenazine derivatives, the shift is intermolecular (Scheme 30).

SCHEME 30 - Proposed Labeling Experiment to Determine if the Alkyl-Shift is Intra- or Intermolecular



Mechanistically, it was hoped that the benzyne intermediate would be a very clean route to the desired N3-CTV. Models suggested that overlap of the benzyne orbitals would be ideal for the final cyclization step of the linear synthesis. However, when NMR spectra from the benzyne reactions are compared with those of the purified N,N'-dimethyl N3-CTV target molecule isolated from Buchwald-Hartwig N-arylation conditions, there is no trace of the 9-membered cyclophane that is detected in the crude mixtures.

Attempted macrocyclization through a benzyne intermediate however did efficiently produce the alkyl-shifted phenazine derivatives. The alkyl-shifted phenazine derivative has been isolated in 78-98% depending on the halogen and alkyl group present. The alkyl shift appears to be dependent upon two factors: the halogen present and the alkyl group employed as the protecting group for the internal nitrogen. It has been hypothesized that when the double-methylated chloro triarylamine derivative is subjected to benzyne conditions, dealkylation occurs by an intermolecular S_N2 process and is not dependent on the formation of the benzyne intermediate. On the other hand, when the fluoro triaryl derivative containing an n-butyl group protecting the internal nitrogen is subjected to benzyne conditions, it appears that the butyl shift is dependent on prior benzyne formation. Further studies will be conducted in order to determine if the alkyl shift is the result of an intermolecular or intramolecular mechanism.

CHAPTER 5

DERIVATIVES OF N3-CTV AND FUTURE WORK

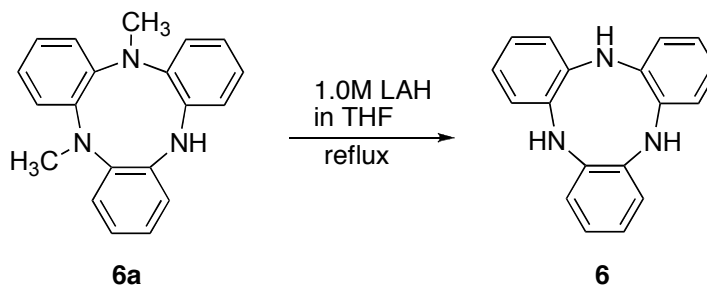
Demethylation

The goal of this research was to synthesize tribenzo-1,4,7-triazacyclononatriene, N3-CTV, and derivatives thereof. With the N,N'-dimethyl N3-CTV in hand, efforts were focused on the dealkylation of the N,N'-dimethyl N3-CTV derivative in order to obtain the tris (NH) N3-CTV **6**. Common demethylation conditions include a strong acid, HCl or HBr, and heat wherein demethylation occurs *via* an S_N2 mechanism after protonation of the nitrogen. The N,N'-dimethyl N3-CTV was subjected to treatment with HBr in AcOH at reflux.¹¹⁵ The reaction led to degradation of the starting material presumably due to protons adding to the aromatic rings in addition to the aniline. A trace of the presumed mono-demethylated N3-CTV was detected by both TLC and ¹H NMR (δ 2.69) but was not isolated.

We decided to investigate alternative methods for demethylating the N,N'-dimethyl N3-CTV derivative. Recently, there have been several accounts of LAH used for demethylating amines.¹¹⁶⁻¹¹⁸ The mechanism by which demethylation occurs is a 1-step

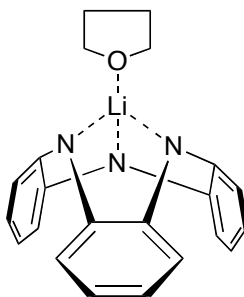
S_N2 by a hydride on the methyl protecting group producing methane gas as a by-product. Unlike HBr or HCl in which a proton can add to either the aniline nitrogen or to the aromatic ring, the hydride ion can only attack the N-methyl group. Thus, by employing LAH we hoped to eliminate the degradation of starting material. Compound **6a** and 1 mL (60 eq) of 1.0 M LAH in THF were brought to reflux for 2 h (Scheme 31). Following the Fieser work-up, TLC showed consumption of SM and a new spot at a low *rf*. Purification by column chromatography gave one compound based on TLC analysis. The ^1H NMR data revealed aromatic peaks representative of a symmetrical *o*-substituted benzene ring showing two sets of doublet of doublets (dd) at δ 7.71 and δ 7.53 ppm due to meta-coupling of the aromatic protons. The disappearance of the methyl peak (δ 2.67) from the dimethyl N3-CTV derivative was also observed. Both the crown and saddle conformers of N3-CTV will have high 3_{cv} symmetry, therefore the conformation of the molecule cannot be determined by NMR. X-ray analysis will be utilized for ultimate structure confirmation of the target cyclophane.

SCHEME 31 - Attempted Demethylation of N,N'-Dimethyl N3-CTV



In addition to the aromatic peaks, both ^1H NMR and ^{13}C NMR indicate a large concentration of aliphatic material, therefore it has been proposed that the N3-CTV may be complexed to a lithium ion which is also complexed to another molecule, for example THF (Figure 12). The ^1H NMR shows a multiplet near δ 4.2 ppm resembling the protons adjacent to the oxygen in THF, except further deshielded. If THF were to be ligated to the lithium, the downfield shift observed in the ^1H NMR is to be expected (Figure 12). Current efforts are focusing on purification and subsequent removal of the hydrocarbon material.

FIGURE 13 - Possible Structure of Lithium-Ligated Species

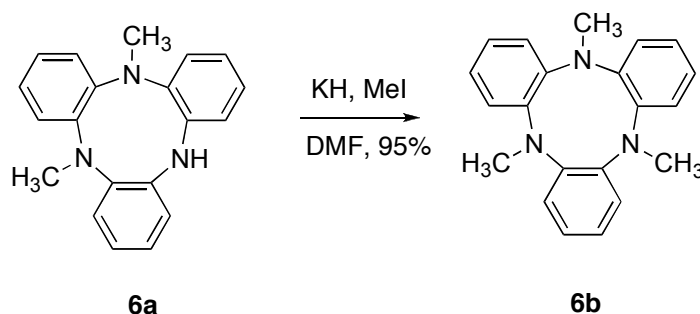


Apex Functionalization and Metal Coordination

One significant improvement offered by the target N3-CTV over the parent CTV is the ability to functionalize the apex of the cyclophane utilizing the nitrogen atoms. Proof of concept was shown by methylation of the third nitrogen utilizing previously established conditions. KH and MeI in DMF at rt efficiently afford the trimethyl N3-CTV **6b** in 95% yield (Scheme 32). ^1H NMR reveals the high 3_{cv} symmetry with

chemical shifts δ 6.90 (12H, s), δ 2.91 (9H, s) manifesting by the similarity of protons ortho and meta to the nitrogen, leading to a fortuitous singlet for all 12 aromatic protons.

SCHEME 32 - Synthesis of the Trimethyl N3-CTV Derivative



Derivation on the apex nitrogens can enable the N3-CTV to be attached to surfaces as well as form lariat complexes. Furthermore, apex functionalization may enable changing of the overall properties of the macromolecule including solubility, hydrophilicity and liquid crystallinity. For example, enhanced water solubility may be accomplished by attaching a carboxylic acid or an amine moiety to one or more apical nitrogens. Our group has recently shown that a lipoic acid side-arm appended to CTV-oxime enables attachment of the cyclophane onto a gold surface. When the CTV-modified surface was exposed to an organic solution containing C_{60} molecules, we were able to detect encapsulation of C_{60} presumably by two CTV-oxime molecules. Similarly, by incorporating apex-modified thiol derivatives onto N3-CTV, we should be able to attach the N3-CTV cyclophane to gold nanoparticles and gold surfaces. The ability to

Apex modified N3-CTV derivatives may have biological uses similar to that of TACN. Recall that several TACN derivatives are currently being used as metal chelators for MRI contrast agents which bind Gd(III), and RIT drugs that bind Lu(III) and Bi(III) and have side-arm moieties that are critical for function.^{55, 57} Future work will incorporate different functional groups on the apex nitrogens in order to mimic TACN derivatives already serving as biologically-active ligands. For example, figure 13 shows two clinically approved hepatobiliary TACN derivatives BOP-DTPA **39** and EOB-DTPA **40** currently being used as Gd-complexed MRI contrast agents.⁵⁵

39 BOP-DTPA

40 FOB-DTPA

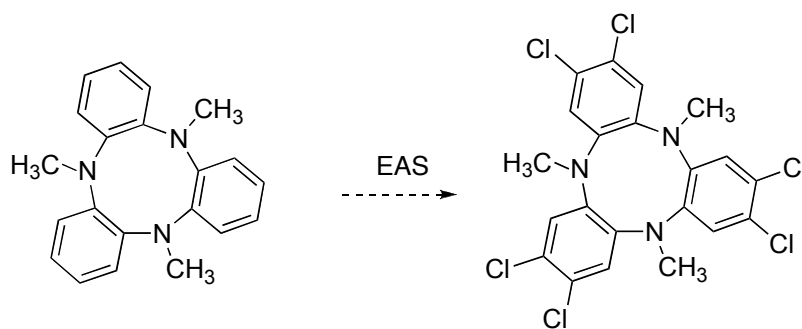
Both BOP-DTPA and EOB-DTPA are taken up by normal hepatocytes in addition to cancerous cells. This characteristic is speculated to be due to the aromatic side arm which binds to the cytosolic protein in liver cells enabling better contrast between healthy

and tumorous liver cells.⁵⁵ The rigidity and aromaticity of N3-CTV with the appropriate functionalization on the nitrogens can enable N3-CTV derivatives to potentially serve as Gd-complexed MRI contrast agents.

In addition to MRI contrast agents, Brechbiel and co-workers are currently exploring RIT drugs of similar TACN derivatives. Their development of C-NETA incorporates both a macrocyclic and a lariat side chain for metal binding. The acyclic side-arm is intended to “capture” and initiate coordination to the metal.⁵⁷

Additionally, we will try to functionalize the periphery of the molecule through electrophilic aromatic substitution (EAS). Classic EAS conditions, which include a strong Lewis Acid catalyst, have been shown to work on tertiary anilines.¹¹⁹ We will attempt to chlorinate the trimethyl N3-CTV by EAS (Scheme 33). The trimethyl derivative will be used in order to avoid electrophilic attack directly on the aniline nitrogens. Formation of the hexachloro derivative would offer a significant advantage, especially in terms of separation. The hexachloro N3-CTV will enable modification on the periphery of N3-CTV as with the parent CTV enabling the formation of more complex cryptands and could enable the preparation of derivatives that have crystalline properties.

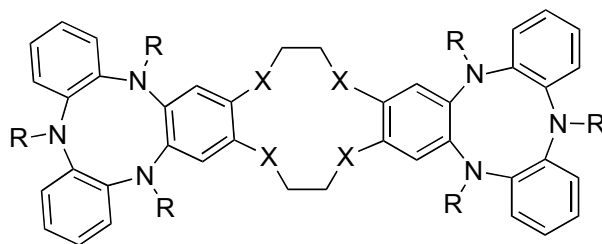
SCHEME 33 - Proposed Electrophilic Aromatic Substitution of N3-CTV



Further exploitation of N3-CTV will include metal-binding studies. It is proposed that the crown-conformer of N3-CTV may be stabilized by chelating metals that prefer tetrahedral geometries. Complexation to a metal will allow the molecule to be used in a variety of ways, for example, as a redox-dependent switch enabling modulation of the cyclophanes binding properties. In order to determine if N3-CTV will bind to metals, we will first conduct a simple binding study with lithium salts. Proton and lithium NMR analysis will show whether binding has occurred if a difference in the chemical shifts of bound versus unbound N3-CTV is observed.

We will also explore building molecular tweezers from the N3-CTV scaffold. Molecular tweezers or clips are noncyclic compounds which contain cavities of flexible size and been shown to be effective synthetic receptors.¹²⁰ Rigid molecular tweezers have been prepared from supramolecular scaffolds including Troeger's base¹²¹ and from Kagan's ether,¹²² that have been shown to bind aromatic substrates. N3-CTV will be synthesized with functionalization on the periphery of one benzene ring in order to form dimeric molecular tweezers (Figure 14).

FIGURE 15 - Structure of Dimeric Molecular Tweezers



Molecular tweezers of N3-CTV can adapt either a *syn* or *anti* orientation with respect to the two bowl units. When the tweezers are in the presence of a tight-binding guest it is hoped that the equilibrium will shift towards the *syn* conformation mimicking the induced-fit process of an enzyme binding a substrate. The size of the linker can also be tunable to encapsulate guests of different sizes.

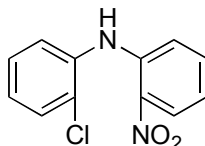
We have shown that the synthesis of the triazaortho cyclophane, N,N'-dimethyl N3-CTV **6a**, can be achieved in 7 steps: palladium catalyzed C-N amination, followed by alkylation and reduction is reiterated in order to obtain the triaryl precursor to the final palladium-catalyzed cyclization to the 9-membered cyclophane. The synthesis of the novel azacyclophane, N3-CTV, will greatly contribute to the area of supramolecular chemistry by providing many distinct advantages over the parent CTV including greatly enhanced water solubility. The incorporation of the apical nitrogens of the N3-CTV scaffold will allow functionalization at the apex, unlike the parent CTV that is mainly functionalized along the periphery. Functionalization of the apex nitrogens can change the molecule's overall physical properties and also enable attachment of N3-CTV onto solid surfaces such as gold. In addition, the apex nitrogens can also complex to metals, allowing stabilization of the crown conformer. Continued progress in the area of

supramolecular chemistry will provide information in the understanding of guest-host chemistry with applications in synthetic receptor design, liquid crystals and human health

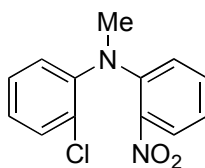
CHAPTER 6

EXPERIMENTAL

All solvents and reagents were used without further purification unless otherwise noted. All solvents were distilled prior to use. All Pd-catalyzed and Cu-catalyzed reactions were conducted under an inert atmosphere of argon. All other reactions were conducted under a nitrogen atmosphere. Sorbent Technologies silica gel 60 A, 40 – 75 μm (200 x 400 mesh) was used for column chromatography. Sorbent Technologies aluminium-backed Silica gel 200 μm plates were used for TLC. ^1H NMR spectra were obtained utilizing either a Varian INOVA 300 or Varian GEMINI 2000 300 MHz spectrometer with trimethylsilane (TMS) as the internal standard. ^{13}C NMR were obtained using either a Varian INOVA 300 or Varian GEMINI 2000 spectrometer at 75 MHz. CEM Discover[®] Microwave Model # 908005 was used in all MW reactions.

(2'-Chlorophenyl)-(2-nitrophenyl)-amine (17)

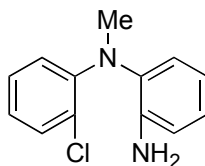
Compound **17** was synthesized according to the general procedures outlined by Tietze *et al.*⁸⁶ A pressure tube was charged with o-nitroaniline (0.690 g, 5 mmol), o-bromochlorobenzene (0.60 mL, 5 mmol), Pd(dba)₂ (0.144 g, 5%), BINAP (0.233 g, 7.5%), Cs₂CO₃ (3.26 g, 10 mmol) and toluene (10 mL). The mixture was purged with Ar for 10 min at rt and the pressure tube was sealed. The reaction was placed in a pre-heating oil bath. The temperature was brought to 120°C and the reaction stirred for 24 h. TLC showed complete consumption of o-nitroaniline and the reaction mixture was filtered through a pad of SiO₂ using 5/5/90 EA/DCM/PE as the eluent. The solvent was removed under vacuum and no further purification was needed to give the product as an orange solid (1.24 g, 100%). ¹H NMR matched the reported values.

2-Chloro-N-methyl-N-(2-nitrophenyl)aniline (18)

Following the general procedure of Wilshire,⁹² compound **17** (1.25 g, 5 mmol) was stirred at rt in acetone (16 mL). Freshly crushed KOH (1.23 g, 22.0 mmol) was added to the stirring mixture. After the reaction was brought to reflux, Me₂SO₄ (2.18 mL, 23

mmol) was added dropwise via syringe over 10 min. The mixture was allowed to stir at reflux for 1 h. The reaction was cooled to rt and 20 mL of 10 M NaOH was added to the solution. After 1 hr the mixture was quenched with 10 mL H₂O and extracted 3 x 10 mL DCM. The organic layers were combined and dried over Na₂SO₄. The solvent was removed under vacuum and the mixture was placed in an 80°C oil bath under vacuum to remove excess Me₂SO₄. No further purification was needed to obtain the desired as a brown solid (1.31 g, 100%). mp 73-75 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.68 (1H, dd, J= 8.1, 1.5 Hz), 7.54 (1H, ddd, J= 8.7, 7.3, 1.7 Hz), 7.42 (1H, dd, J= 7.8, 1.5 Hz), 7.19 (1H, dd, J=7.7, 1.7 Hz), 7.14-7.11 (2H, m), 7.06 (1H, dd, J=7.7, 1.9 Hz), 7.0 (1H, ddd, J=8.2, 7.3, 1.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 143.0, 133.2, 131.3, 130.9, 128.7, 127.9, 126.7, 126.2, 125.9, 120.8, 120.6, 41.1; IR (CDCl₃): 1520 (NO₂); HRMS (MH⁺) calcd for C₁₃H₁₁O₂N₂Cl 263.0509, found 263.0604.

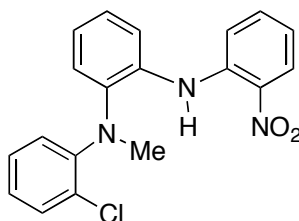
N¹-(2-Chlorophenyl)-N¹-methylbenzene-1,2-diamine (19)



Following the general procedure of Sanz,⁹³ CuCl (0.137 g, 1.38 mmol) was added to a stirring solution of compound **18** (0.121 g, 0.46 mmol) in MeOH (4.6 mL) at rt. KBH₄ (0.174 g, 3.22 mmol) was then added in portions. The reaction stirred at rt until the solution became clear, 2-4 hr. The reaction was quenched with H₂O and extracted 3 x 15 mL 90/10 EA/DCM. The organic layers were combined and dried over Na₂SO₄ and the

solvent was removed to give the desired product as a brown oil (0.107 g, 100%). ^1H NMR (300MHz, CDCl_3) δ 7.32 (1H, dd, J = 7.8, 1.4 Hz), 7.25 (1H, dd, J = 7.3, 1.7 Hz), 7.22 (1H, dd, J = 7.1, 1.7 Hz), 7.16 (1H, dd, J = 8.0, 1.6 Hz), 7.00-6.95 (2H, m), 6.76 (1H, ddd, J =9.3, 7.7, 1.4 Hz), 6.67 (1H, ddd, J = 8.9, 7.6, 1.5 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 142.2, 136.9, 130.7, 130.68, 127.4, 125.5, 123.6, 121.9, 118.6, 115.8, 41.1; IR (CDCl_3): 3440 (NH_2), 3351 (NH_2); HRMS (MH^+) calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{Cl}$ 233.0767, found 233.0791.

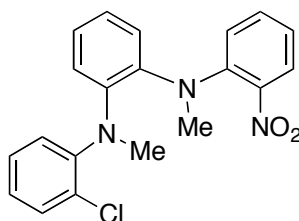
N^1 -(2-Chlorophenyl)- N^1 -methyl- N^2 -(2-nitrophenyl)benzene-1,2-diamine (20)



Compound **19** (0.842 g, 3.62 mmol), o-iodonitrobenzene (1.35 g, 5.43 mmol), $\text{Pd}_2(\text{dba})_3$ (0.104 g, 5% mol), BINAP (0.170 g, 7.5%), Cs_2CO_3 (2.35 g, 7.42 mmol) and 12 mL of toluene were placed in a pressure tube. The mixture was purged with Ar at rt for 15 min. The tube was then sealed and placed in a pre-heated oil bath at 80-90°C for 30 h. When TLC showed consumption of **19**, the reaction mixture was filtered through silica gel eluting with 90/10 EA/DCM. The solvent was then removed under vacuum. The product was then purified by column chromatography on silica gel eluting with 1/99 Et_2O /PE to afford the desired product as a red crystalline solid (0.785 g, 80%). mp 141-145 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.03 (1H, bs), 8.07 (1H, dd, J =8.7, 1.5 Hz), 7.32-7.19 (4H,

m), 7.12-6.99 (5H, m), 6.90 (1H, ddd, $J = 8.0, 6.9, 2.2$ Hz), 6.68 (1H, ddd, $J = 8.4, 6.9, 1.2$ Hz), 3.16 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 147.2, 145.1, 142.4, 135.2, 131.6, 130.7, 129.5, 127.4, 126.5, 126.5, 126.0, 124.8, 124.0, 123.2, 121.7, 117.0, 115.8, 40.6; IR (CDCl_3) 3344 (NH), 1503 (NO_2); HRMS (MH^+) calcd for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_2\text{Cl}$ 354.1009, found 354.0961.

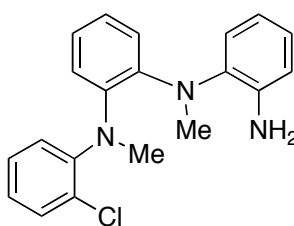
N^1 -(2-Chlorophenyl)- N^1, N^2 -dimethyl- N^2 -(2-nitrophenyl)benzene-1,2-diamine (21**)**



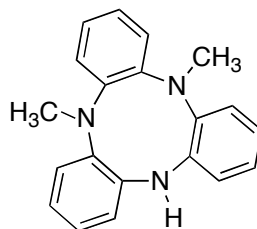
A solution of compound **20** (0.405 g, 1.14 mmol) in 4 mL of DMF was added to KH (0.46 g, 3.42 mmol). Upon addition, the solution went from orange to deep purple. The mixture was stirred at rt for 10 min. MeI (0.4 mL, 5.7 mmol) was added dropwise via syringe. The reaction was stirred at rt until the solution returned to a yellow color. The reaction was then quenched with H_2O and extracted 3 x 15 mL EA. The organic layers were combined and washed 3 x 15 mL H_2O , brine then H_2O again to remove excess DMF. The organic layer was then dried over MgSO_4 , the solvent was removed under reduced pressure to give the desired product as a yellow powder with no further purification necessary (0.362 g, 86%). ^1H NMR (300MHz, CDCl_3) δ 7.63 (1H, dd, $J = 8.0, 1.7$ Hz), 7.36 (1H, ddd, $J = 8.8, 7.3, 1.8$ Hz), 7.29-7.19 (2H, m), 7.12 (1H, dd, $J = 8.2, 1.7$ Hz), 7.07-6.92 (5H, m), 6.88 (1H, ddd, $J = 8.2, 7.3, 1.2$ Hz), 6.81 (1H, dd, $J = 7.8, 1.2$

Hz), 3.32 (3H, s), 3.27 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 146.5, 143.5, 142.1, 138.8, 132.7, 131.0, 128.7, 127.6, 126.2, 124.2, 124.1, 123.7, 123.1, 120.4, 118.8, 38.5, 38.1; IR (CDCl_3) 1520 (NO_2); HRMS (MH^+) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_2\text{Cl}$ 368.1166, found 368.1091.

N^1 -(2-Aminophenyl)- N^2 -(2-chlorophenyl)- N^1, N^2 -dimethylbenzene-1,2-diamine (22a)

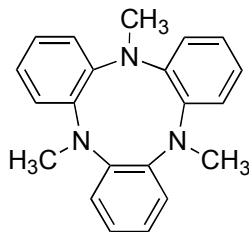


Following the general procedure of Sanz,⁹³ CuCl (0.460 g, 4.65 mmol) was added to a stirring solution of compound **21** (0.570 g, 1.55 mmol) in MeOH (15.5 mL) at rt. KBH_4 (0.836 g, 15.5 mmol) was then added in portions. The reaction stirred at rt until the solution became clear, 2-4 hr. The reaction was then quenched with H_2O and extracted 3 x 30 mL 90/10 EA/DCM. The organic layers were combined and dried over Na_2SO_4 and the solvent was removed to give the desired product as a brown oil, (0.450 g, 86%). ^1H NMR (300MHz, CDCl_3) δ 7.3 (1H, dd, J = 8.0, 1.9 Hz), 7.15 (1H, 8.5, 7.3, 1.7 Hz), 7.06-6.88 (7H, m), 6.83-6.73 (2H, m), 6.60 (1H, dd, J =7.3, 1.5 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 147.0, 143.4, 142.2, 141.1, 136.7, 131.1, 128.2, 127.3, 124.6, 124.4, 124.3, 123.4, 123.4, 123.2, 122.6, 122.5, 118.7, 116.1, 39.4, 38.6; IR (CDCl_3) 3441 (NH_2), 3368 (NH_2); HRMS (MH^+) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_3\text{Cl}$ 338.1424, 338.1379.

N-Methyl-2-(10-methylphenazin-5(10H)-yl)aniline (6a)

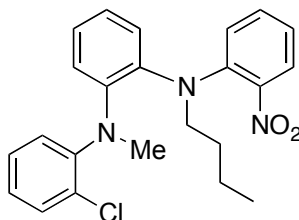
Compound **22a** (0.090 g, 0.27 mmol), Pd(dba)₂ (0.016 g, 10% mol), BINAP (0.034 g, 20% mol), Cs₂CO₃ (0.132 g, 0.41 mmol) in 3 mL of 1:1 toluene/t-BuOH were added to a 10 mL microwave tube. The mixture was purged with Ar for 5 min while stirring at rt. The MW settings were as follows; P = 250W, Time = 60 min, Temp = 130°C; PSI = 250. The reaction mixture was checked by TLC after each 60 min run. When TLC showed consumption of **22a**, 240 min total, the mixture was filtered through a pad of silica gel with 90/10 EA/DCM. The solvent was removed under reduced pressure. The product was then purified by column chromatography eluting with DCM/PE gradient to give the final product as a white powder (41mg, 50%). ¹H NMR (300MHz, CDCl₃) δ 7.05-6.95 (6H, m), 6.87 (1H, d, J= 1.1 Hz), 6.84 (1H, d, J= 1.1 Hz), 6.75-6.73 (4H, m), 5.82 (1H, bs), 2.68 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 144.2, 141.4, 140.2, 127.8, 126.1, 121.9, 121.1, 118.4, 117.5, 39.9; IR (CDCl₃) 3382 (NH), 1499 (C=C); HRMS (MH⁺) calcd for C₂₀H₁₉N₃ 302.1579, found 302.1573.

5,10,15-Trimethyl-10,15-dihydro-5*H*-tribenzo[*b,e,h*][1,4,7]triazonine



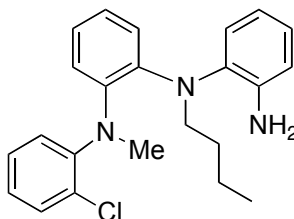
A solution of compound **6a** (0.018 g, 0.07 mmol) in 0.2 mL of DMF was added to KH (0.028 g, 0.21 mmol). Upon addition, effervescence ensued and the solution turned a pale pinkish-purple color. The mixture was stirred at rt until effervescence ceased, about 5 min, and MeI (0.022 mL, 0.35 mmol) was added dropwise via syringe. The reaction was allowed to stir at rt for 2 h, during which the solution became faint yellow in color. The reaction mixture was quenched with deionized H₂O and extracted with EA (3 x 10 mL). The organic layers were combined and dried over Na₂SO₄, the solvent was removed under reduced pressure to give the product as a pale yellow oil. (0.021 g, 95% yield) ¹H NMR (300MHz, CDCl₃) δ 6.92 (12H, s), 2.93 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 122.9, 121.0, 40.6; HRMS (MH⁺) calcd for C₂₁H₂₁N₃ 316.1808, found 316.1799.

N¹-Butyl-N²-(2-fluorophenyl)-N²-methyl-N¹-(2-nitrophenyl)benzene-1,2-diamine(25)

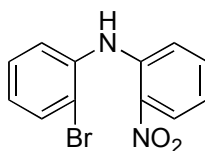


A solution of compound **20** (0.100 g, 0.28 mmol) in 2 mL of DMF was added to KH (0.112 g, 0.83 mmol). Upon addition, the solution went from orange to deep purple. The mixture was stirred at rt for 10 min. n-butyl bromide (0.3 mL, 2.8 mmol) was added dropwise via syringe. The reaction was brought to 80°C and stirred until the solution returned to an orange color, 3 h. The reaction was then quenched with H₂O and extracted 3 x 15 mL EA. The organic layers were combined and washed 3 x 25 mL H₂O, brine then H₂O again to remove excess DMF. The organic layer was then dried over MgSO₄, the solvent was removed under reduced pressure. The crude product was purified by column chromatography using a gradient of EA/PE as the eluent to give the desired product as a red oil. (0.065 g, 56%). ¹H NMR (300MHz, CDCl₃) δ 7.57 (1H, dd, J = 8.0, 1.7 Hz), 7.40 (1H, ddd, J = 8.7, 7.2, 1.6 Hz), 7.24 (1H, dd, J = 15.4, 1.4 Hz), 7.21 (1H, dd, J = 14.8, 1.7 Hz), 7.06 (1H, dd, J = 8.1, 1.5 Hz), 7.02-6.87 (6H, m), 6.76 (1H, dd, J = 8.2, 1.7 Hz), 3.77 (2H, t, J = 8.1 Hz), 3.31 (3H, s), 1.6 (2H, m), 1.29 (2H, m), 0.90 (3H, t, J = 7.4, 7.1 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 146.67, 132.78, 132.26, 131.04, 130.06, 128.36, 128.26, 127.81, 127.53, 126.29, 125.90, 125.80, 124.11, 123.98, 123.68, 120.74, 120.65, 119.11, 49.82, 33.58, 29.01, 20.14, 13.98 IR (CDCl₃) 2958 (C-H), 2929 (C-H), 2871 (C-H), 2817 (C-H), 1524 (NO₂); HRMS (M+H)⁺ calcd for C₂₃H₂₄N₃O₂Cl 410.1630, found 410.1640.

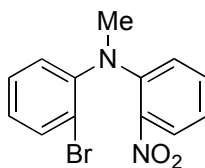
N¹-(2-Aminophenyl)-N¹-butyl-N²-(2-chlorophenyl)-N²-methylbenzene-1,2-diamine(26)



Following the general procedure of Sanz,⁹³ CuCl (0.06 g, 0.06 mmol) was added to a stirring solution of compound **25** (0.079 g, 0.2 mmol) in MeOH (2.0 mL) at rt. KBH₄ (0.108 g, 2.0 mmol) was then added in portions. The reaction stirred at rt until the solution became clear, 2-4 hr. The reaction was then quenched with H₂O and extracted 3 x 15 mL 90/10 EA/DCM. The organic layers were combined and dried over Na₂SO₄ and the solvent was removed to give the desired product as a brown oil. (0.063 g, 82%). ¹H NMR (300MHz, CDCl₃) δ 7.29 (1H, dd, J = 7.8, 1.5 Hz), 7.15-7.00 (4H, m), 6.95-6.84 (5H, m), 6.73-6.62 (2H, m), 3.46 (5H, t, J = 7.8 Hz), 3.2 (3H, s), 1.42-1.32 (2H, m), 1.25-1.16 (2H, m), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 147.19, 143.26, 143.18, 142.38, 135.85, 131.20, 127.45, 127.28, 125.30, 124.80, 124.49, 123.70, 122.97, 118.39, 116.35, 50.60, 40.30, 30.22, 20.49, 14.06; IR (CDCl₃) 3436 (NH₂), 3375 (NH₂), 2956 (C-H), 2929 (C-H), 2869 (C-H), 1491 (C=C); HRMS (M+H)⁺ calcd for C₂₃H₂₆N₃Cl 380.1888, found 380.1892.

(2'-Bromophenyl)-(2-nitrophenyl)-amine(17a)

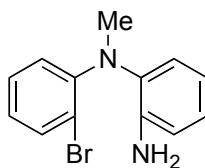
Compound **17a** was synthesized according to the general procedures outlined by Tietze *et al.*⁸⁶ A pressure tube was charged with o-nitroaniline (0.690 g, 5 mmol), o-bromiodobenzene (0.64 mL, 5 mmol), Pd(dba)₂ (0.144 g, 5%), BINAP (0.233 g, 7.5%), Cs₂CO₃ (3.26 g, 10 mmol) and toluene (10 mL). The mixture was purged with Ar for 10 min at rt and the pressure tube was sealed. The reaction was placed in a pre-heating oil bath. The temperature was brought to 120°C and the reaction stirred for 24 h. TLC showed complete consumption of o-nitroaniline and the reaction mixture was filtered through a pad of SiO₂ using 10/90 DCM/EA as the eluent. The solvent was removed under vacuum and product was purified by column chromatography using 1/99 Et₂O/PE as the eluent to afford the desired product as bright orange crystals (1.31 g, 90% yield). Spectra match reported values.

2-Bromo-N-methyl-N-(2-nitrophenyl)aniline (18a)

Following the general procedure of Wilshire⁹², compound **17a** (0.235 g, 0.80 mmol) was dissolved at rt in acetone (16 mL). Freshly crushed KOH (0.98 g, 3.52 mmol) was added

to the stirring mixture. After the reaction was brought to reflux, Me₂SO₄ (0.35 mL, 3.68 mmol) was added dropwise via syringe over 10 min. The mixture was allowed to stir at reflux for 1 h. The reaction was cooled to rt and 20 mL of 10 M NaOH was added to the solution. After 1 hr the mixture was quenched with 10 mL H₂O and extracted 3 x 10 mL DCM. The organic layers were combined and dried over Na₂SO₄. The solvent was removed under vacuum and the mixture was placed in an 80°C oil bath under vacuum to remove excess Me₂SO₄. No further purification was necessary to obtain the desired product as an orange solid (0.241 g, 98%). mp 88-92 °C; ¹H NMR (300MHz, CDCl₃) δ 7.68 (1H, dd, J= 8.2,1.6 Hz), 7.62 (1H, ddd, J = 7.7, 1.7, 0.6 Hz), 7.46 (1H, dt, J = 8.5, 7.0, 1.7 Hz), 7.26 (1H, dd, J= 8.5, 1.7 Hz), 7.12-6.96 (4H, m), 3.3 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 146.5, 142.9, 134.6, 133.1, 128.7, 127.2, 126.6, 126.2, 121.5, 120.6, 120.3, 111.7, 41.4.

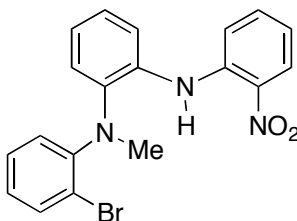
N¹-(2-Bromophenyl)-N¹-methylbenzene-1,2-diamine (19a)



Reduction was accomplished according to the general procedure of Sanz.⁹³ CuCl (0.267 g, 2.7 mmol) was added to a stirring solution of compound **18a** (0.275 g, 0.90 mmol) in MeOH (9.0 mL) at rt. KBH₄ (0.485 g, 9.0 mmol) was then added in portions. The reaction stirred at rt until the solution became clear, 2-4 hr. The reaction was then quenched with H₂O and extracted with 3 x 25 mL 90/10 EA/DCM. The organic layers

were combined and dried over Na₂SO₄ and the solvent was removed to give the desired product as a brown oil (0.155 g, 62%). ¹H NMR (300MHz, CDCl₃) δ 7.18 (2H, dd, J = 7.3, 1.9 Hz), 7.05 (2H, ddd, J = 8.0, 1.6, 1.4 Hz), 6.79-6.72 (3H, m), 6.65 (2H, dd, J = 8.8, 1.1 Hz), 3.77 (2H, bs), 3.18 (3H, s); ¹³C (75 MHz, CDCl₃) δ 148.8, 143.8, 134.2, 129.0, 128.9, 128.0, 127.3, 127.8, 119.2, 117.6, 115.9, 113.4, 38.6.

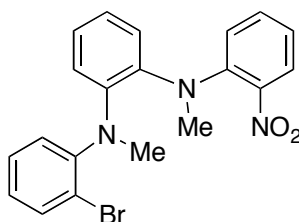
N¹-(2-Bromophenyl)-N¹-methyl-N²-(2-nitrophenyl)benzene-1,2-diamine (20a)



Compound **19a** (0.155 g, 0.56 mmol), o-iodonitrobenzene (0.167 g, 0.67 mmol), Pd(dba)₂ (0.016 g, 5% mol), BINAP (0.026 g, 7.5%), Cs₂CO₃ (0.365 g, 1.12 mmol) and 2 mL of toluene were placed in a pressure tube. The mixture was purged with Ar at rt for 15 min. The tube was sealed and placed in an oil bath, 80-90°C for 30 h. When TLC showed consumption of **19a**, the reaction mixture was filtered through silica gel with 90/10 EA/DCM. The solvent was then removed under vacuum and the product was purified by column chromatography on silica gel eluting with 1/99 Et₂O/PE to afford the product as a red crystalline solid. (0.157 g, 70%) mp 90-92 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.26 (1H, bs), 8.08 (1H, dd, J = 8.5, 1.7 Hz), 7.46 (1H, dd, J = 6.2, 2.5 Hz), 7.2-7.4 (4H, m), 7.13 (2H, ddd, J = 8.8, 7.4, 2.2 Hz), 6.75 (2H, dt, J = 6.9, 1.4 Hz), 6.65 (2H, dd, J = 8.0,

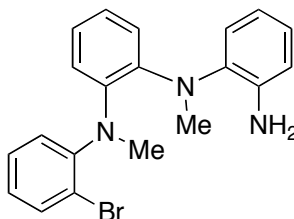
1.1 Hz), 3.23 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 148.6, 142.1, 141.8, 135.6, 135.2, 133.8, 129.0, 127.8, 126.5, 126.0, 125.9, 123.7, 119.1, 117.7, 116.1, 115.1, 39.6

N^1 -(2-Bromophenyl)- N^1 , N^2 -dimethyl- N^2 -(2-nitrophenyl)benzene-1,2-diamine (21a)

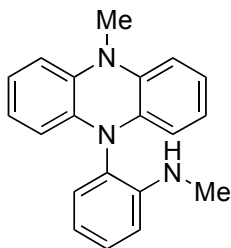


A solution of compound **20a** (0.565 g, 1.42 mmol) in 5.5 mL of DMF was added to KH (0.570 g, 4.26 mmol). The mixture was stirred at rt for 10 min. MeI (0.44 mL, 7.1 mmol) was then added dropwise and the reaction was allowed to stir at rt for 30 min. The reaction was then quenched with H_2O and extracted 3 x 15 mL EA. The organic layers were combined and washed 3 x 25 mL H_2O , brine then H_2O again to remove excess DMF. The organic layer was then dried with MgSO_4 , and the solvent was removed under reduced pressure to give the desired product as an orange solid with no further purification necessary. (0.563 g, 86%); mp 104-107 $^\circ\text{C}$; ^1H NMR (300MHz, CDCl_3) δ 7.58 (1H, dd, J = 8.1, 1.5 Hz), 7.29-7.16 (3H, m), 7.11-7.04 (3H, m), 6.91 (1H, ddd, J = 8.4, 7.4, 1.4 Hz), 6.76 (1H, dd, J = 8.2, 1.1 Hz), 6.70 (1H, tt, J = 7.3, 1.1 Hz), 3.27 (3H, s), 2.82 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 147.7, 144.0, 143.4, 142.8, 140.0, 132.8, 129.0, 128.4, 126.5, 125.3, 124.7, 124.4, 123.5, 121.5, 117.5, 113.9, 42.2, 38.1.

N¹-(2-Aminophenyl)-N²-(2-bromophenyl)-N¹,N²-dimethylbenzene-1,2-diamine (22b)



Following the general procedure of Sanz,⁹³ CuCl (0.576 g, 1.94 mmol) was added to a stirring solution of compound **21a** (0.802 g, 5.82 mmol) in MeOH (20 mL) at rt. KBH₄ (1.05 g, 19.4 mmol) was then added in portions. The reaction stirred at rt until the solution became clear, 2-4 hr. The reaction was then quenched with H₂O and extracted 3 x 40 mL 90/10 EA/DCM. The organic layers were combined and dried over Na₂SO₄ and the solvent was removed to give the desired product as a brown oil (0.679, 92%). The product was a brownish oil (0.422 g, 88%). ¹H NMR (300 MHz, CDCl₃) δ 7.25 (2H), 7.12-7.02 (3H, m), 6.86 (1H, ddd, J = 8.8, 7.3, 2.2 Hz), 6.67-6.56 (4H, m), 6.29 (2H, dd, J = 8.6, 1.0 Hz), 2.25 (5H, s), 2.48 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 147.7, 147.2, 142.3, 138.6, 138.4, 129.9, 128.6, 126.8, 125.3, 123.8, 122.6, 119.0, 118.5, 116.3, 116.2, 112.2, 38.5, 38.0.

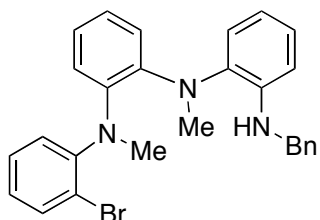
N-Methyl-2-(10-methylphenazin-5(10H)-yl)aniline (24)

In an oven-dried round-bottom flask, KH (0.543 g, 4.06 mmol) was washed 3 x 5 mL dry PE under N₂ at rt. 1 mL of THF was added to the KH and stirred at rt for 5 min.

Diisopropylamine (0.15 mL, 1.0 mmol) was then added to the KH and the mixture stirred at rt for 5 min. Compound **22a** (0.098 g, 0.29 mmol) in THF (5 mL) was added dropwise by syringe to the KDA in THF (1 mL). The mixture was allowed to reflux for 1-2 hr until TLC showed complete consumption of **22a**. The reaction mixture was quenched with 15 mL of H₂O and extracted 3 x 20 mL degassed Et₂O. The organic layers were combined and dried over MgSO₄ and the solvent was removed in vacuo. The desired product was then dissolved in 2-3 mL of Et₂O and 1 equivalent of p-toluenesulfonic acid (0.050 g, 0.29 mmol) was added to form the tosylate salt as clear

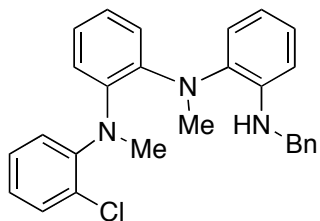
crystals. ¹H NMR (300MHz, CDCl₃) δ 7.33 (1H, ddd, J = 9.2, 7.8, 1.5 Hz), 7.16 (1H, dd, J = 8.1, 1.5 Hz), 6.82 (2H, t, J = 15.7, 7.8 Hz), 6.63 (2H, ddd, J = 9.1, 7.7, 1.4 Hz), 6.41 (2H, ddd, J = 8.7, 7.8, 1.2 Hz), δ 6.34 (2H, dd, J = 7.7, 1.1 Hz), δ 5.82 (2H, dd, J = 7.8, 1.2 Hz), δ 4.45 (1H, bs), 3.01 (3H, s), 2.79 (3H, bs); ¹³C NMR (75 MHz, CDCl₃) δ 146.9, 136.9, 131.1, 129.6, 129.2, 125.5, 121.7, 120.7, 117.5, 111.8, 111.2, 110.9, 30.2, 29.7; HRMS (M^{•+}) calcd for C₂₀H₁₉N₃ 301.1573, found 301.1562.

N¹-(2-Benzylamino)phenyl-N²-(2-bromophenyl)-N¹,N²-dimethylbenzene-1,2-diamine (22d)



The benzyl derivative was synthesized according to the general procedures outlined by Itoh¹²³ *et al.* To a stirring solution of **22b** (0.177 g, 0.46 mmol) in THF (1 mL) was added benzaldehyde (47 μ L, 0.46 mmol). The mixture stirred at rt for 5 min under an argon atmosphere. Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (0.117 g, 0.46 mmol) in THF (1 mL) followed by Sc(OTf)₃ (0.005 g, 2%) in THF (1 mL) were added dropwise to the stirring solution. The mixture stirred overnight at rt under an argon atmosphere. The product was taken up in 10 mL EA and washed 3 x 20 mL with 5% (w/v) NaHCO₃ followed by brine. The organic layer was dried over Na₂SO₄ and solvent was removed in vacuo. Column chromatography eluting with PE afforded the desired product as a light yellow solid (0.149 g, 68%). ¹H NMR (300MHz, CDCl₃) δ 7.34-7.01 (11H, m), 6.89 (1H, ddd, J = 9.1, 7.7, 1.4 Hz), 6.65 (1H, dd, J = 7.7, 1.4 Hz), 6.58–6.50 (1H, m), 6.41 (1H, dd, J = 8.0, 1.1 Hz), 6.30 (2H, d, J = 8.0 Hz), 4.09 (1H, t, J = 10.4, 5.2 Hz), 3.73 (2H, d, J = 5.2 Hz), 3.04 (3H, s), 2.43 (3H, s); ¹³C (75 MHz, CDCl₃) δ 148.7, 147.7, 144.1, 140.0, 138.9, 138.3, 129.9, 128.8, 128.2, 127.0, 126.8, 126.5, 125.6, 123.4, 122.7, 118.5, 116.9, 116.2, 111.6, 110.7, 47.8, 38.6, 37.7.

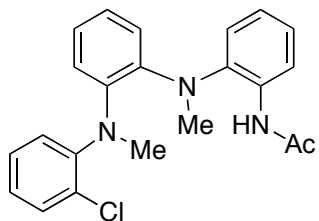
**N¹-(2-Benzylamino)phenyl-N²-(2-chlorophenyl)-N¹,N²-dimethylbenzene-1,2-diamine
(22c)**



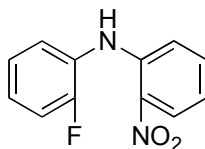
The benzyl derivative was synthesized according to the general procedures outlined by Itoh¹²³ *et al.* To a stirring solution of **22a** (0.071 g, 0.21 mmol) in THF (1 mL) was added benzaldehyde (26 μ L, 0.25 mmol). The mixture stirred at rt for 5 min under an argon atmosphere. AcOH (0.12 μ L, 0.21 mmol) and Na(OAc)₃BH (0.067 g, 0.315 mmol) in THF (1 mL) were added to the stirring solution. The mixture stirred at reflux for 3 h. The reaction was quenched with sat. NaHCO₃ and extracted with Et₂O 3 x 10 mL. The organic layers were combined and the solvent was removed under reduced pressure. The crude product was purified by column chromatography eluting with 1/99 Et₂O/PE to afford the desired product as a light yellow solid (0.02 g, 22%). ¹H NMR (300 MHz, CDCl₃) δ 7.19 (1H, d, J = 1.9 Hz), δ 7.17 (1H, d, J = 1.9 Hz), δ 7.09-6.84 (13H, m), δ 6.68 (1H, ddd, J = 8.9, 7.6, 1.4 Hz), δ 6.44 (1H, dd, J = 8.0, 1.4 Hz), δ 4.27 (1H, t, J = 5.5 Hz), δ 4.09 (2H, d, J = 5.5 Hz), δ 3.20 (3H, s), δ 3.09 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 147.5, 144.2, 142.8, 142.4, 139.7, 136.4, 131.2, 131.22, 131.18, 128.4, 128.3, 127.2, 126.9, 126.7, 124.7, 124.67, 124.4, 123.6, 123.57, 123.3, 123.0, 122.9, 122.4, 116.7, 110.6, 39.8, 39.2

N-(2((2-((2-Chlorophenyl)(methyl)amino)phenyl)(methyl)amino)phenyl)acetamide

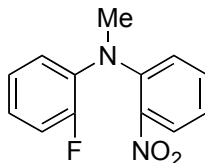
(22e)



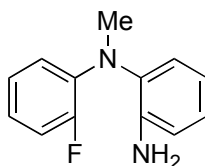
In a screw-cap vial, compound **22a** (0.063 g, 0.19 mmol) and Et₃N (0.12 mL, 0.86 mmol) in 1 mL THF were stirred at 0°C for 5 min. To the stirring mixture, AcCl (0.1 mL, 0.86 mmol) was added dropwise and a ppt immediately formed. The ice bath was removed and the mixture stirred for 2 h at rt. The reaction mixture was taken up in DCM and the organic layer was washed with 1 N HCl (2 x 5 mL), deionized H₂O (2 x 5 mL), then brine 5 mL. The organic layer was dried over Na₂SO₄, the solvent is removed under reduced pressure to give the crude oil. Purification was accomplished by column chromatography using silica gel and eluting with a EA/PE. The gradient started with 30/70 EA/PE and increased to 50/50 EA/PE. The solvent was removed under reduced pressure to give the product as a light brown oil. (0.032 g, 44% yield). ¹H NMR (300MHz, CDCl₃) δ 8.13 (1H, d, J = 8.0 Hz), 7.87 (1H, bs), 7.3 (1H, dd, J = 8.4, 1.5 Hz), 7.19 (1H, ddd, J = 9.3, 7.7, 1.6 Hz), 7.13-6.93 (9H, m), 2.95 (3H, s), 2.83 (3H, s), 1.88 (3H, s).

(2'-Fluorophenyl)-(2-nitrophenyl)-amine (27)

Compound **27** was synthesized according to the general procedures outlined by Tietze *et al.*⁸⁶ A pressure tube was charged with o-nitroaniline (0.690 g, 5 mmol), o-fluoriodobenzene (0.70 mL, 6 mmol), Pd(dba)₂ (0.144 g, 5%), BINAP (0.233 g, 7.5%), Cs₂CO₃ (3.26 g, 10 mmol) and toluene (10 mL). The mixture was purged with Ar for 10 min at rt and the pressure tube was sealed. The reaction was placed in a pre-heating oil bath. The temperature was brought to 120°C and the reaction stirred for 24 h. TLC showed complete consumption of o-nitroaniline and the reaction mixture was filtered through a pad of SiO₂ using 10/90 DCM/EA as the eluent. The solvent was removed under reduced pressure and product was purified by column chromatography using 1/99 Et₂O/PE as the eluent to afford the final product as orange crystals (0.915 g, 78% yield). ¹H NMR (300MHz, CDCl₃) δ 8.24 (1H, dd, J = 8.7, 1.5 Hz), 7.44-7.37 (2H, m), 7.24-7.18 (3H, m), 7.08 (1H, dt, J = 2.9, 1.5, 1.4 Hz), 6.83 (1H, ddd, J= 7.2, 7.0, 1.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 158.32, 155.03, 142.25, 135.68, 126.85, 125.95, 124.72, 118.06, 116.85, 116.59, 115.98; IR (CDCl₃) 3345 (NH), 1609 (C=C), 1577 (C=C), 1509 (NO₂); HRMS (M+H)⁺ calcd for C₁₂H₉N₂O₂F 233.0721, found 233.0727.

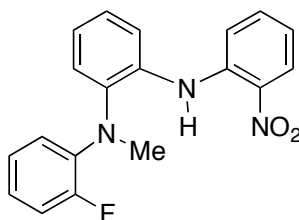
2-Fluoro-N-methyl-N-(2-nitrophenyl)aniline (28)

Compound **27** (0.122 g, 0.525 mmol) was stirred at rt in acetone (2 mL). Freshly crushed KOH (0.130 g, 2.31 mmol) was added to the stirring mixture.⁹² The reaction was brought to reflux and Me₂SO₄ (0.23 mL, 2.42 mmol) was added dropwise via syringe. The mixture was allowed to reflux for 1 h. The reaction was cooled to rt and 1 mL of 10 M NaOH was added to the solution. After 1 h the mixture was quenched with 2 mL H₂O and extracted with 3 x 10 mL of 90/10 EA/MC. The organic layers were combined and dried over MgSO₄. The solvent was removed under reduced pressure and the mixture was placed in an 80°C oil bath under vacuum to remove excess Me₂SO₄. No further purification was needed to obtain the product as a brown oil. (0.122 g, 95% yield). ¹H NMR (300MHz, CDCl₃) δ 7.73 (1H, dd, J = 7.8, 1.7 Hz), 7.5 (1H, ddd, J = 8.2, 7.4, 1.7 Hz), 7.24 (1H, dd, J = 8.4, 1.2 Hz), 7.09-6.94 (5H, m), 3.33 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 157.85, 154.55, 143.02, 133.28, 125.81, 125.14, 124.61, 123.51, 122.14, 116.75, 41.05; IR (CDCl₃) (C=C), 1522 (NO₂), 1501 (NO₂); HRMS (M+H)⁺ calcd for C₁₃H₁₁N₂O₂F 247.0877, found 247.0871.

N¹-(2-Fluorophenyl)-N¹-methylbenzene-1,2-diamine (29)

CuCl (0.150 g, 1.50 mmol) was added to a stirring solution of compound **28** (0.122 g, 0.5 mmol) in dry MeOH (5.0 mL) at rt. KBH₄ (0.270 g, 5.0 mmol) was then added in portions. The reaction effervesced and a black ppt formed upon each addition. Once all the KBH₄ was added, the reaction continued to stir at rt until the solution became clear in color, 2-4 h. The reaction was quenched with H₂O and extracted with 3 x 10 mL 90/10 EA/MC. The organic layers were combined and dried over Na₂SO₄. The solvent was removed under vacuum to give the produce as a light brown oil. (0.096 g, 89% yield). ¹H NMR (300MHz, CDCl₃) δ 7.06-6.85 (6H, m), 6.76 (1H,dd, J = 7.8, 1.2 Hz), 6.70 (1H, ddd, J = 8.8, 7.7, 1.4 Hz), 3.91 (2H, bs), 3.15 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 156.53, 153.26, 142.15, 126.15, 124.71, 124.20, 121.68, 119.64, 118.76, 116.35, 116.08, 115.80, 39.97; IR (CDCl₃) 3452 (NH₂), 3351 (NH₂), 1608 (C=C), 1500 (C=C); HRMS (M+H)⁺ calcd for C₁₃H₁₃N₂F 217.1136, found 217.1133.

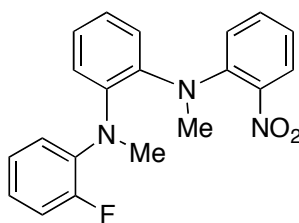
N¹-(2-Fluorophenyl)-N¹-methyl-N²-(2-nitrophenyl)benzene-1,2-diamine (30)



Compound **29** (0.096 g, 0.44 mmol), o-iodonitrobenzene (0.132 g, 0.53 mmol), Pd(dba)₂ (0.013 g, 5% mol), BINAP (0.021 g, 7.5% mol), Cs₂CO₃ (0.215 g, 0.66 mmol) and 2 mL of toluene were placed in a pressure tube. The mixture was purged with Ar at rt for 15 min. The pressure tube was then sealed and placed in a pre-heated oil bath at 130°C for

24 h. When TLC showed consumption of **29**, the reaction mixture was filtered through a pad of SiO₂ with 90/10 EA/MC. The solvent was removed under reduced pressure and the resulting product was purified by column chromatography eluting with 1/99 Et₂O/PE to afford the desired product as a red oil. (0.082 g, 55% yield). ¹H NMR (300 MHz, CDCl₃) δ 9.12 (1H, bs), 8.05 (1H, dd, J = 8.5, 1.7 Hz), 7.34-7.05 (6H, m), 6.86-6.83 (4H, m), 6.69 (1H, ddd, J = 8.5, 7.1, 1.4 Hz), 3.21 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ xxx.xx, xxx.xx, 144.39, 142.30, 135.13, 126.39, 125.66, 124.21, 123.68, 123.55, 122.69, 122.36, 117.14, 116.36, 116.09, 115.76, 40.63; IR (CDCl₃) 3343 (NH), 1615 (C=C), 1593 (C=C), 1573 (C=C), 1501 (NO₂); HRMS (M+H)⁺ calcd for C₁₉H₁₆N₃O₂F 338.1299, found 338.1306.

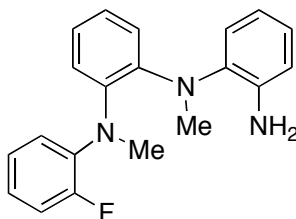
N¹-(2-Bromophenyl)-N¹,N²-dimethyl-N²-(2-nitrophenyl)benzene-1,2-diamine (31)



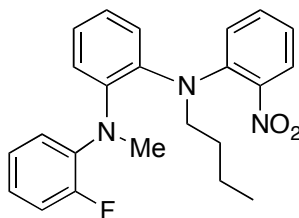
A solution of compound **30** (0.082 g, 0.24 mmol) in 2 mL of DMF was added to KH (0.100 g, 0.72 mmol). Upon addition, the solution changed color from orange to deep purple. The mixture was stirred at rt for 10 min. MeI (1.0 mL, 1.2 mmol) was added dropwise via syringe. The reaction continued to stir until the solution became bright yellow in color, 2 h. The reaction was then quenched with H₂O and extracted with 3 x 10 mL 90/10 EA/MC. The organic layers were combined and washed with 3 x 20 mL H₂O, then brine. The organic layer was dried over Na₂SO₄, the solvent was removed under

reduced pressure to give the desired product as a yellow solid with no further purification necessary. (0.082 g, 97% yield). ^1H NMR (300MHz, CDCl_3) δ 7.62 (1H, dd, J = 8.2, 1.7 Hz), 7.34 (1H, ddd, J = 8.8, 7.4, 1.9 Hz), 7.1-6.75 (10H, m), 3.22 (3H, s), 3.14 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ ; IR (CDCl_3) 1606 (C=C), 1591 (C=C), 1568 (C=C), 1522 (NO_2), 1500 (NO_2); HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_2\text{F}$ 352.1456, found 352.1463.

N^1 -(2-aminophenyl)- N^2 -(2-fluorophenyl)- N^1, N^2 -dimethylbenzene-1,2-diamine (32)

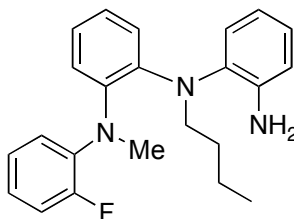


See Synthesis of **29**. ^1H NMR (300 MHz, CDCl_3) δ 7.12 (2H, m), 7.00 (2H, m), 6.92 (3H, m), 6.78 (2H, m), 6.65 (2H, m), 6.56 (1H, dd, J = 9.2, 1.5 Hz), 3.17 (2H, bs), 3.08 (3H, s), 2.97 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 155.68, 152.42, 145.24, 141.66, 140.81, 137.37, 137.07, 127.02, 125.59, 124.94, 124.00, 123.54, 122.60, 120.05, 119.86, 119.33, 118.75, 116.36, 116.10, 39.80, 38.44; IR (CDCl_3) 3435 (NH_2), 3346 (NH_2), 1612 (C=C), 1501 (NO_2); HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{N}_3\text{F}$ 322.1714 found 322.1728.

N¹-butyl-N²-(2-fluorophenyl)-N²-methyl-N¹-(2-nitrophenyl)benzene-1,2-diamine (33)

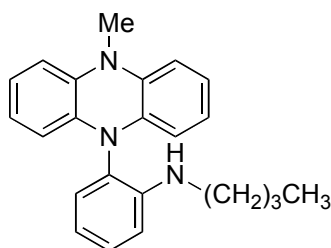
A solution of compound **30** (0.102 g, 0.30 mmol) in 2 mL of DMF was added to KH (0.121 g, 0.91 mmol). Upon addition, the solution went from orange to deep purple. The mixture was stirred at rt for 10 min. n-butyl bromide (0.32 mL, 3.0 mmol) was added dropwise via syringe. The reaction was heated to 80°C and stirred until the solution returned to an orange color 3 h. The reaction was then quenched with H₂O and extracted 3 x 15 mL DCM. The organic layers were combined and washed 3 x 25 mL H₂O, brine then H₂O again to remove excess DMF. The organic layer was then dried over MgSO₄, the solvent was removed under reduced pressure. The crude product was purified by column chromatography using a gradient of EA/PE as the eluent to give the desired product as a red oil. (0.063 g, 53%). ¹H NMR (300 MHz, CDCl₃) δ 7.57 (1H, dd, J = 8.1, 1.5 Hz), 7.34 (1H, ddd, J = 8.7, 7.3, 1.7 Hz), 7.11-6.77 (9H, m), 3.59 (2H, t, J = 15.9, 8.0 Hz), 3.06 (3H, d, J = 1.1 Hz), 1.65-1.54 (2H, m), 1.30 (2H, s, 22.4, 14.8, 7.3 Hz), 0.88 (3H, t, J = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 132.61, 132.25, 132.01, 130.05, 129.52, 129.09, 128.31, 127.81, 125.81, 125.55, 125.07, 124.05, 122.56, 121.27, 120.81, 120.33, 116.40, 116.13, 52.46, 39.16, 29.68, 20.29, 13.92; HRMS (M+H)⁺ calcd for C₂₃H₂₄N₃O₂F 394.1925, found 394.1939.

N¹-(2-Aminophenyl)-N¹-butyl-N²-(2-fluorophenyl)-N²-methylbenzene-1,2-diamine(34)



See synthesis of **22a**. (0.06 g, 100%) ¹H NMR (300MHz, CDCl₃) δ 7.18-6.99 (5H, m), 6.95-6.86 (2H, m), 6.78-6.71 (2H, m), 6.66-6.60 (2H, m), 6.50 (1H, ddd, J = 9.6, 8.2, 1.8 Hz), 3.38 (2H, t, J = 7.8 Hz), 3.20 (2H, bs), 2.90 (3H, s), 1.51-1.41 (2H, m), 1.32-1.20 (2H, m), 0.86 (3H, t, J = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ ; HRMS (M+H)⁺ calcd for C₂₃H₂₆N₃F 364.2184, found 364.2175.

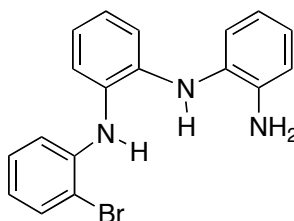
N-Butyl-2-(10-methylphenazin-5(10*H*)-yl)aniline (36)



In an oven-dried RBF, 2 mL of THF and DIPA (0.11 mL, 0.80 mmol) was added to KH (0.300 g, 2.24 mmol) at rt. The mixture stirred for 10 min and compound **34** in 3 mL of THF was added dropwise via syringe. The reaction mixture was brought to reflux for 2 h. The reaction mixture was cooled to rt and quenched with H₂O. The product was extracted with 3 x 20 mL of 90/10 EA/MC. The organic layers were combined and dried

over Na₂SO₄, the solvent was removed under reduced pressure to give the product as a green oil. (0.048 g, 87% yield). ¹H NMR (300MHz, CDCl₃) δ 7.3 (1H, ddd, J = 8.5, 7.3, 2.3), 7.16, (1H, dd, J = 7.7, 1.4), 6.83-6.75 (2H, m), 6.62 (2H, t, J = 7.7), 6.41 (1H, t, 7.7), 6.34 (1H, d, J = 7.8), 5.81 (2H, dd, J = 7.8, 1.2), 4.37 (1H, bs), 3.12 (2H, t, J = 7.1), 3.02 (3H, s), 1.55-1.43 (2H, m), 1.36-1.21 (2H, m), 0.85 (3H, t, J = 7.3); ¹³C NMR (75 MHz, CDCl₃) δ ; IR (CDCl₃) 3415 (NH), 2965 (C-H), 2962 (C-H), 2870 (C-H), 1607 (C=C), 1508 (C=C), 1482 (C=C); HRMS (M^{•+}) calcd for C₂₃H₂₅N₃ 343.2043, found 343.2046.

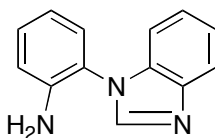
N¹-(2-Aminophenyl)-N²-(2-bromophenyl)benzene-1,2-diamine (14)



A pressure vessel was charged with 2,2'-dibromodiphenylamine (0.328 g, 1 mmol), o-phenylenediamine (0.54 g, 5 mmol), Pd(OAc)₂ (0.007 g, 5 mol %), DPEPhos (0.03 g, 7.5 mol %) and p-xylene (3 mL). The mixture stirred under and inert atm of Ar for 30 min at 80°C. NaOtBu (0.150 g, 1.5 mmol) in p-xylene (3 mL) was added to the stirring mixture. The pressure vessel was sealed and the reaction stirred at 140°C for 48 h. The reaction mixture was allowed to cool to rt and filtered through a pad of celite with Et₂O. Purification by column chromatography using 25/75 EA/PE as the eluent gave the product an oil. (16 mg, 6% yield). ¹H NMR (300MHz, CDCl₃) δ 7.49 (1H, dd, J = 8.0, 1.4), 7.31 (1H, dd, J = 8.2, 1.4), 7.17 - 7.11 (3H, m), 7.03 (1H, ddd, J = 8.8, 7.6, 1.4),

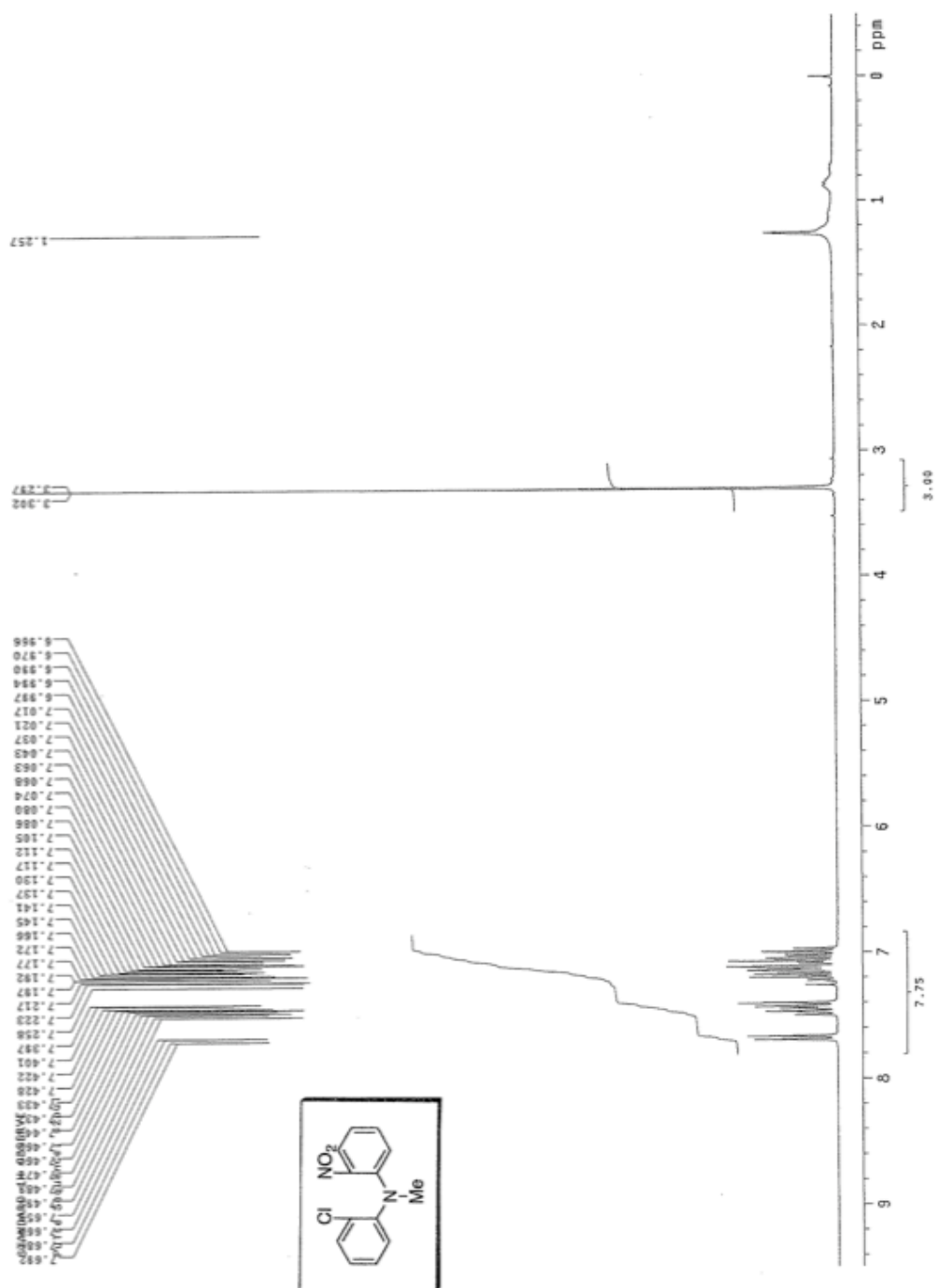
6.82 – 6.69 (4H,m), 6.62 (1H), 6.49 (1H, t, J = 4.1, 2.1), 6.42 (1H, dd, J = 8.0, 1.7),
6.01 (1H, bs), 5.91 (1H, bs), 3.84 (2H, bs).

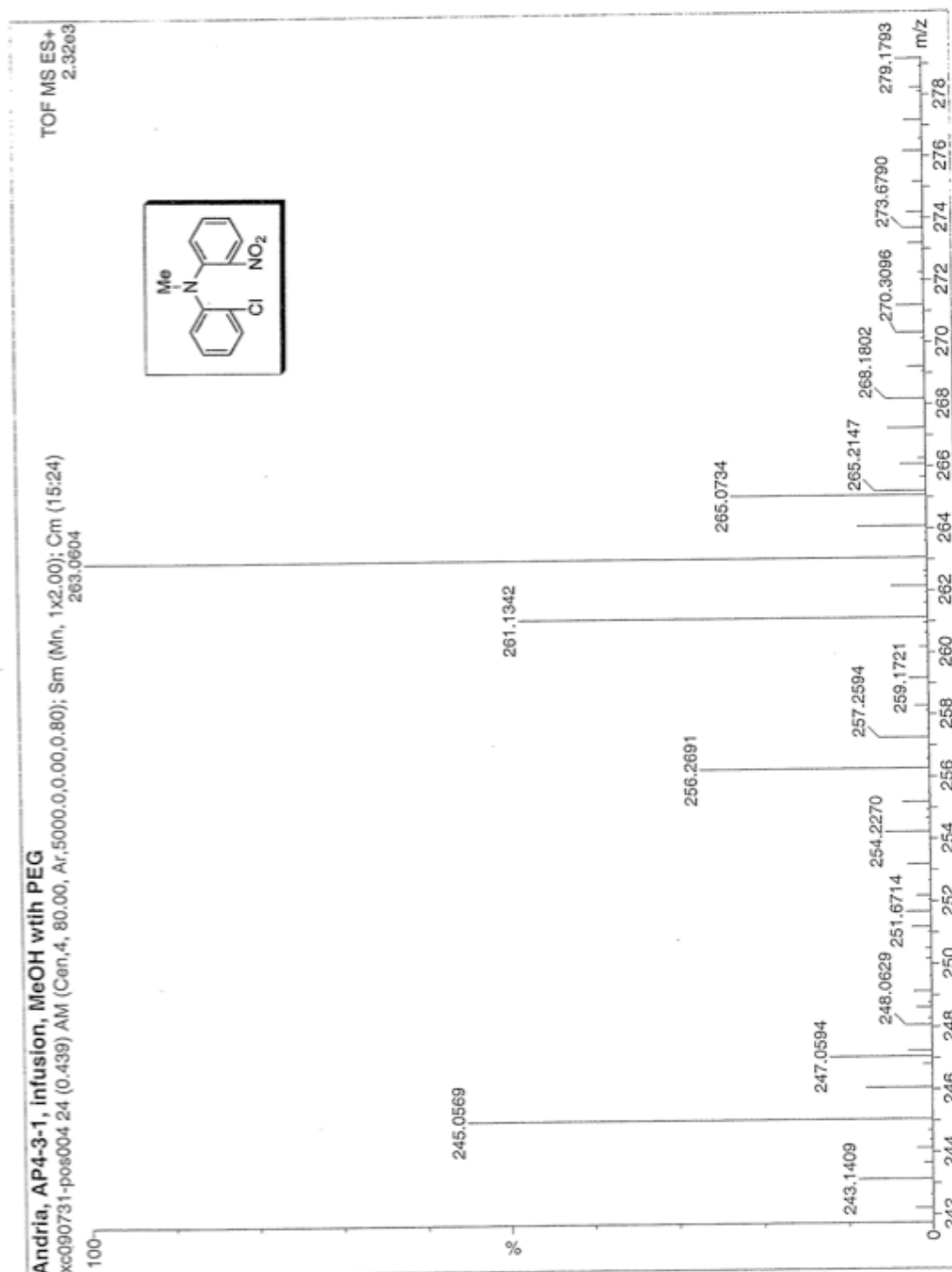
1-(1*H*-Benzo[d]imidazol-1-yl)aniline (15)

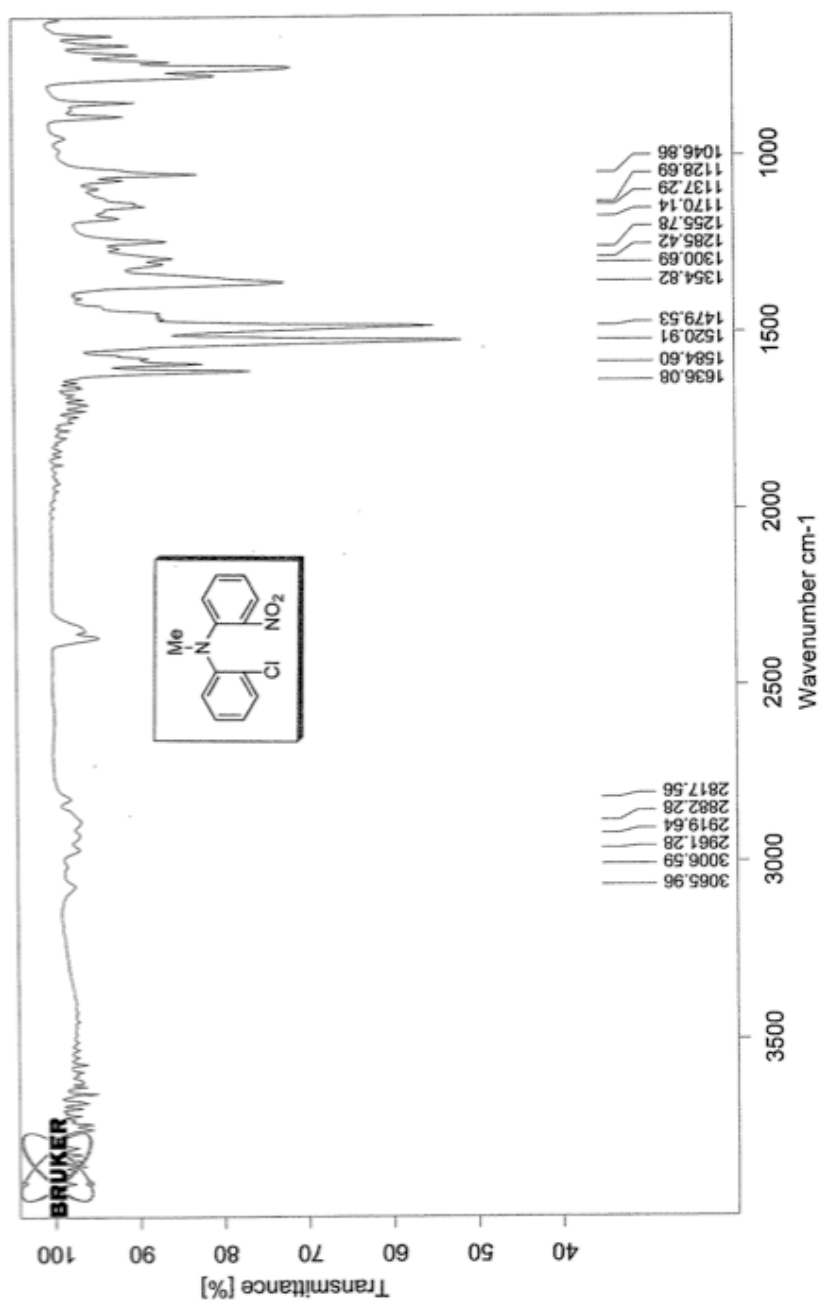


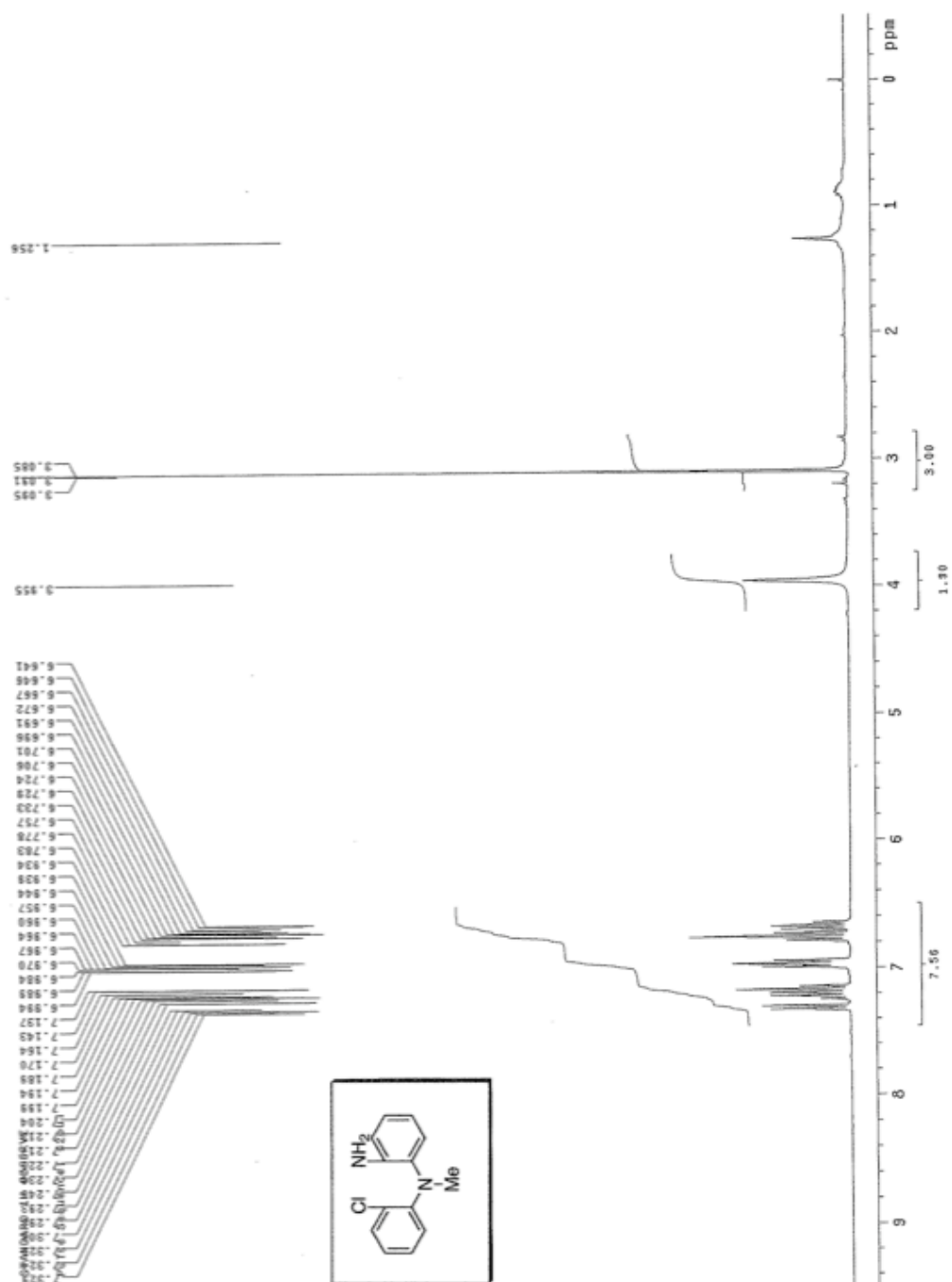
A 25 mL RBF was charged with 2,2'-diaminodiphenylamine (0.110 g, 0.55 mmol), HC(OMe)₂NMe₂ (0.073 mL, 0.55 mmol), and p-xylene (1.1 mL). The mixture was brought to reflux and stirred o.n. TLC revealed the presence of SM and another eq. of HC(OMe)₂NMe₂ was added to the mixture and again the mixture was refluxed o.n. TLC revealed consumption of SM. The solvent was removed under reduced pressure and purification by column chromatography 1/99 NH₃ in MeOH/DCM gave the product as a light brown foam. (32 mg, 28% yield.). ¹H NMR (300MHz, CDCl₃) δ 8.02 (1H, bs), 7.9 (1H, d, J = 8.4), 7.41-7.18 (6H, m), 6.91 (1H, t, J = 14.4, 7.2), 3.63 (2H, bs).

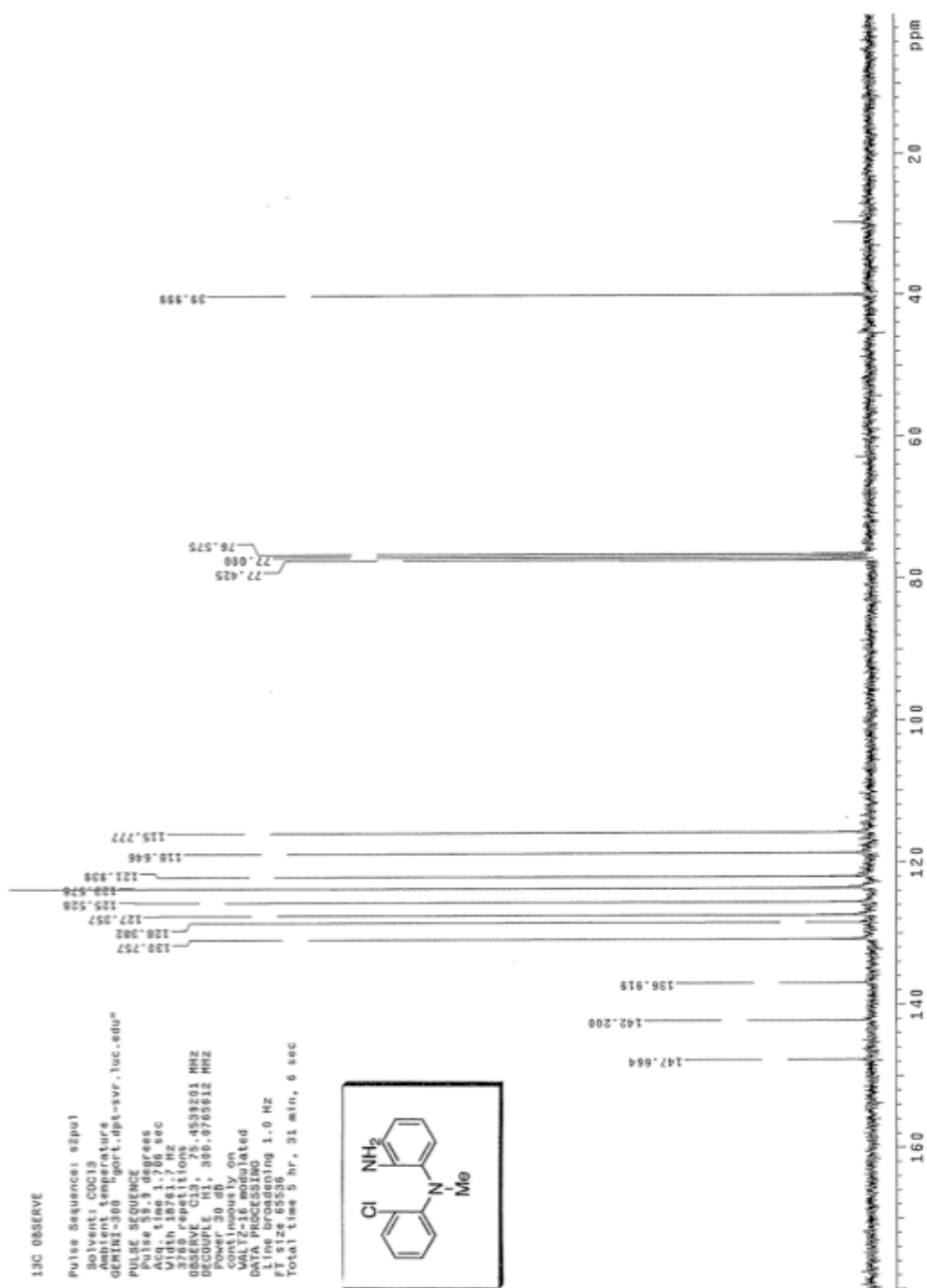
APPENDIX A
SUPPLEMENTAL DATA

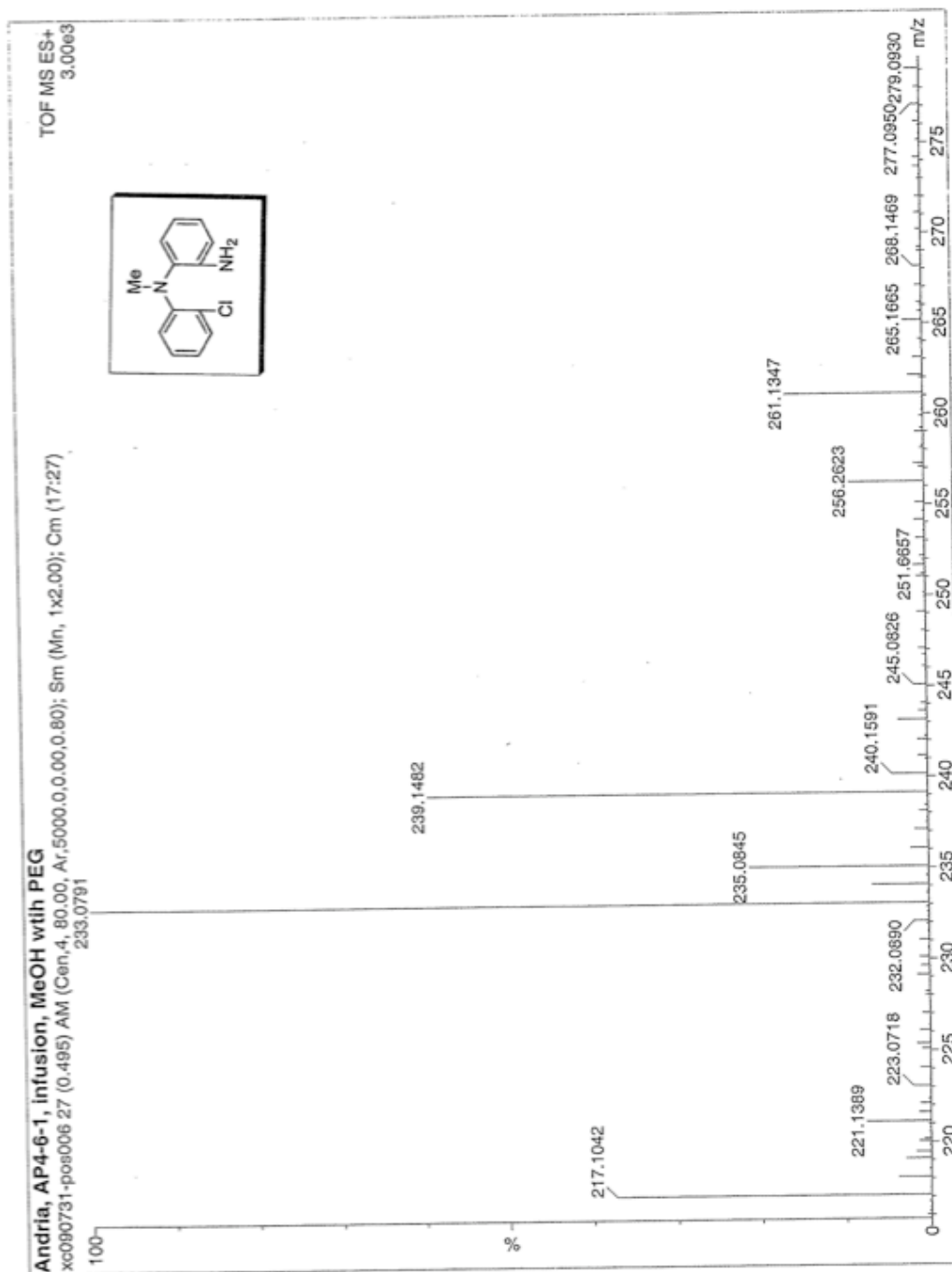


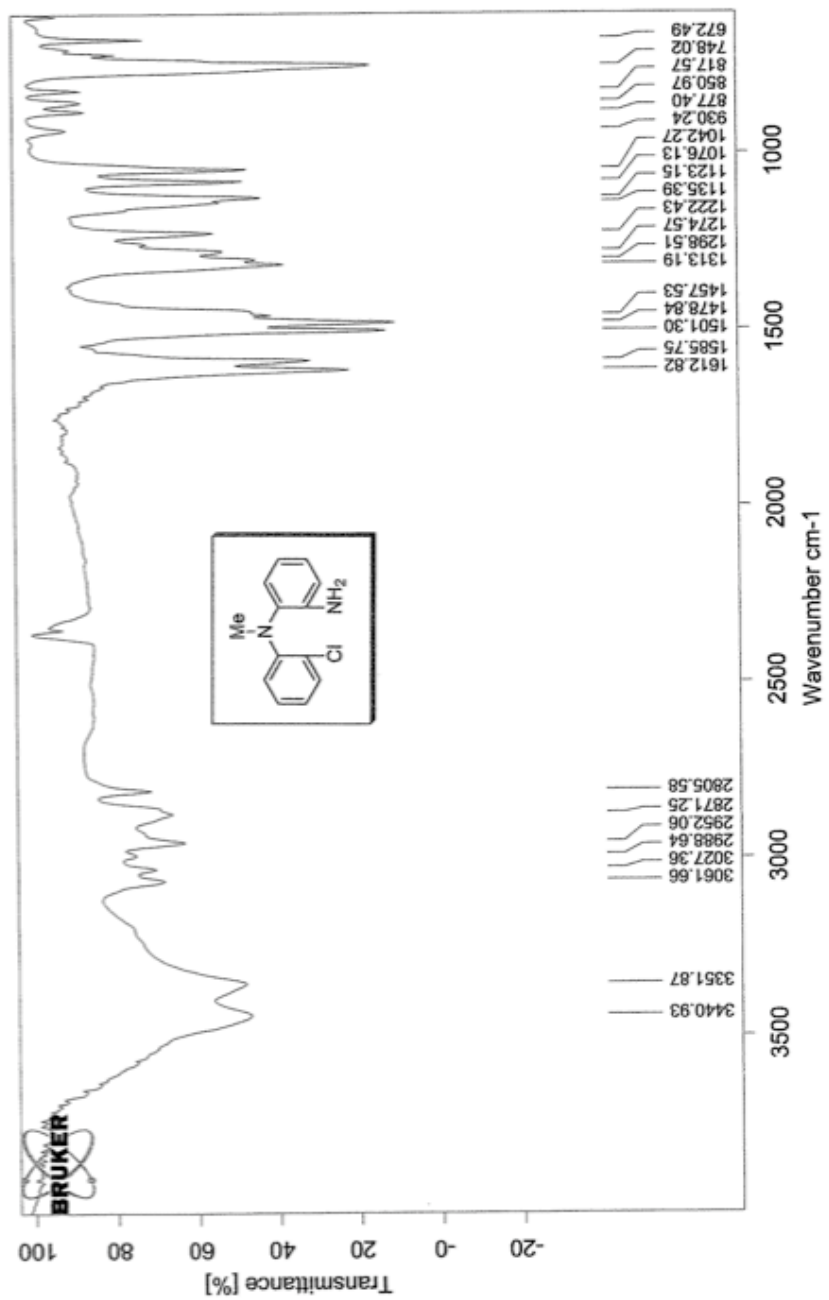


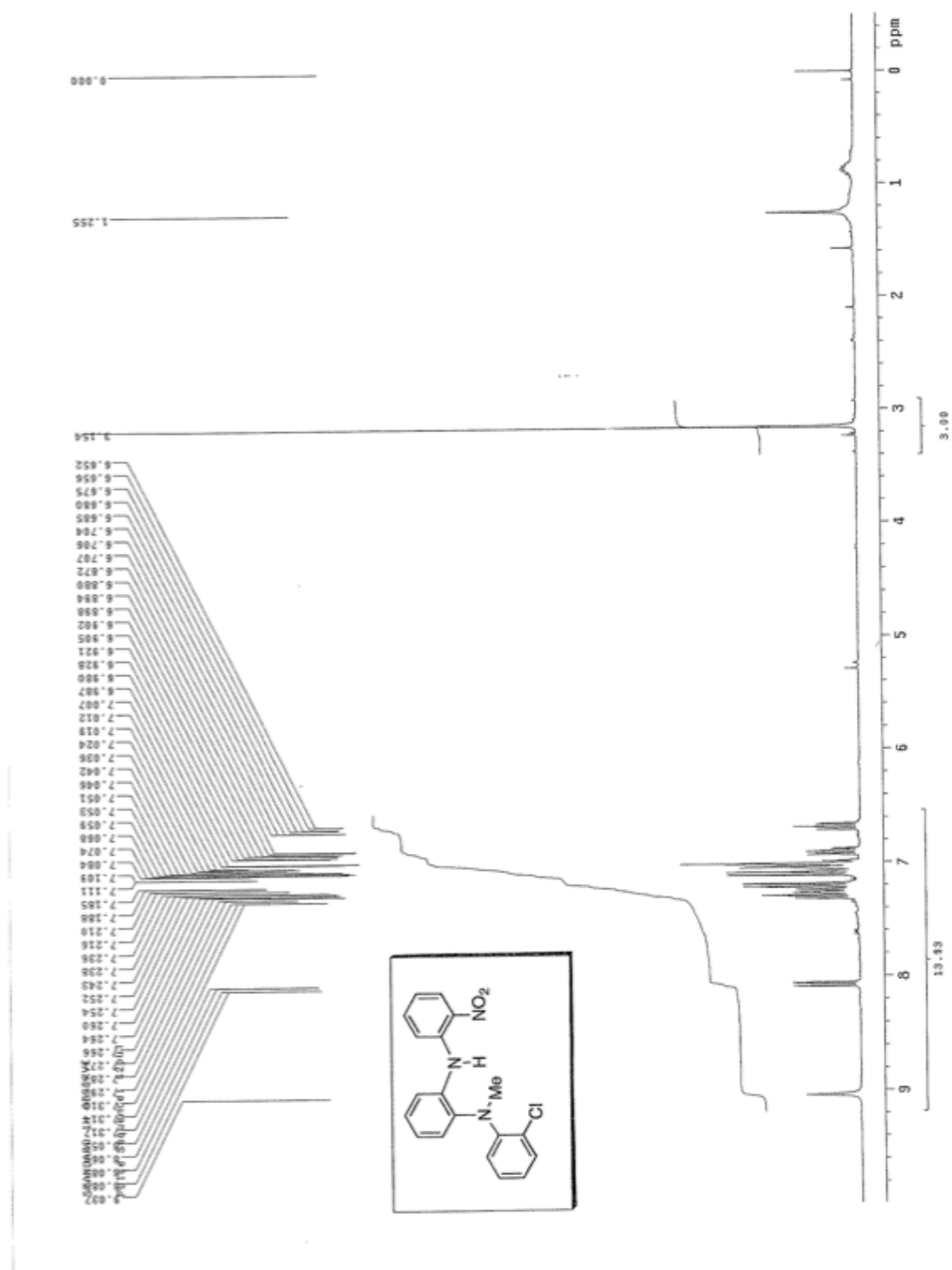


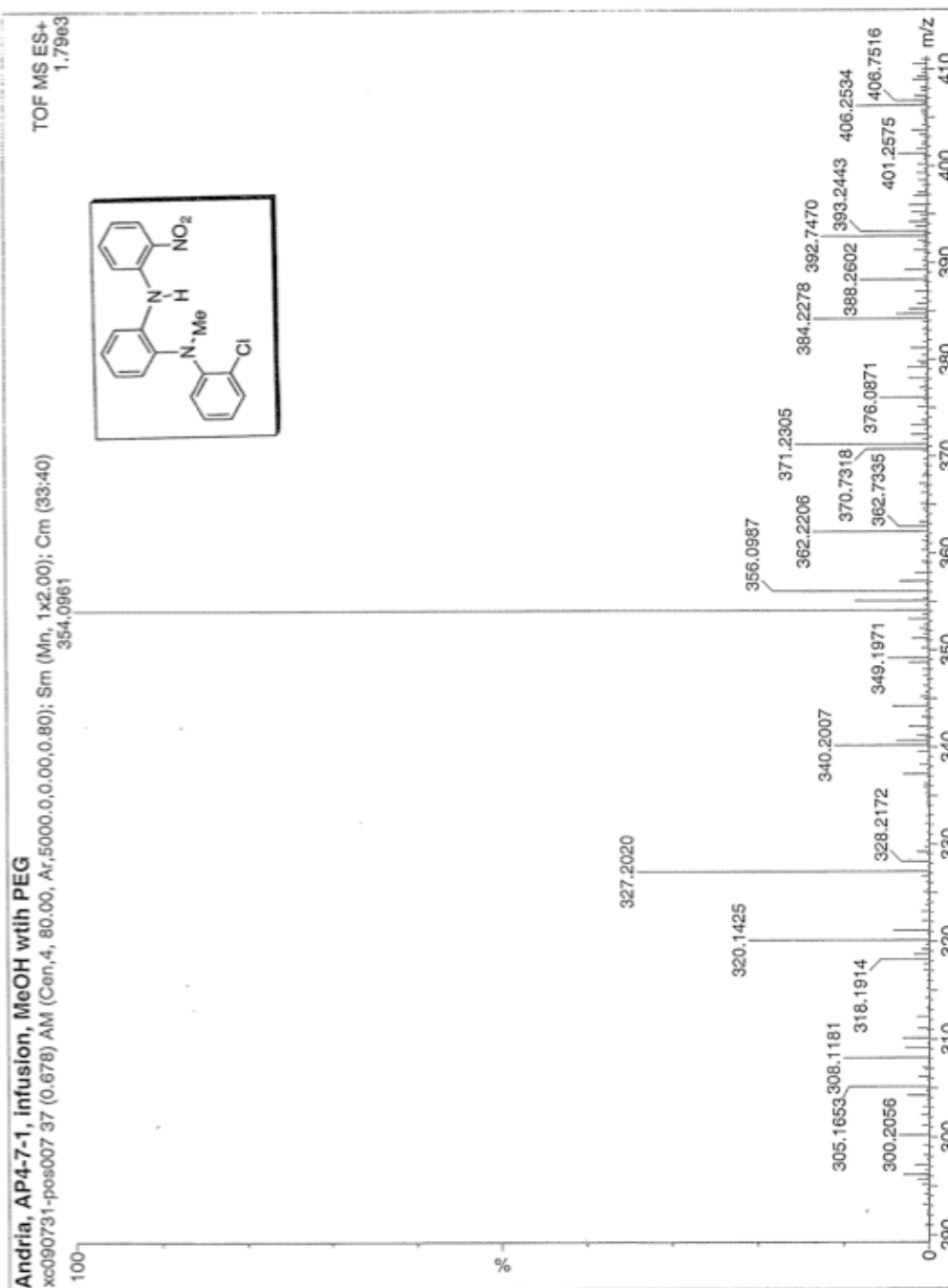


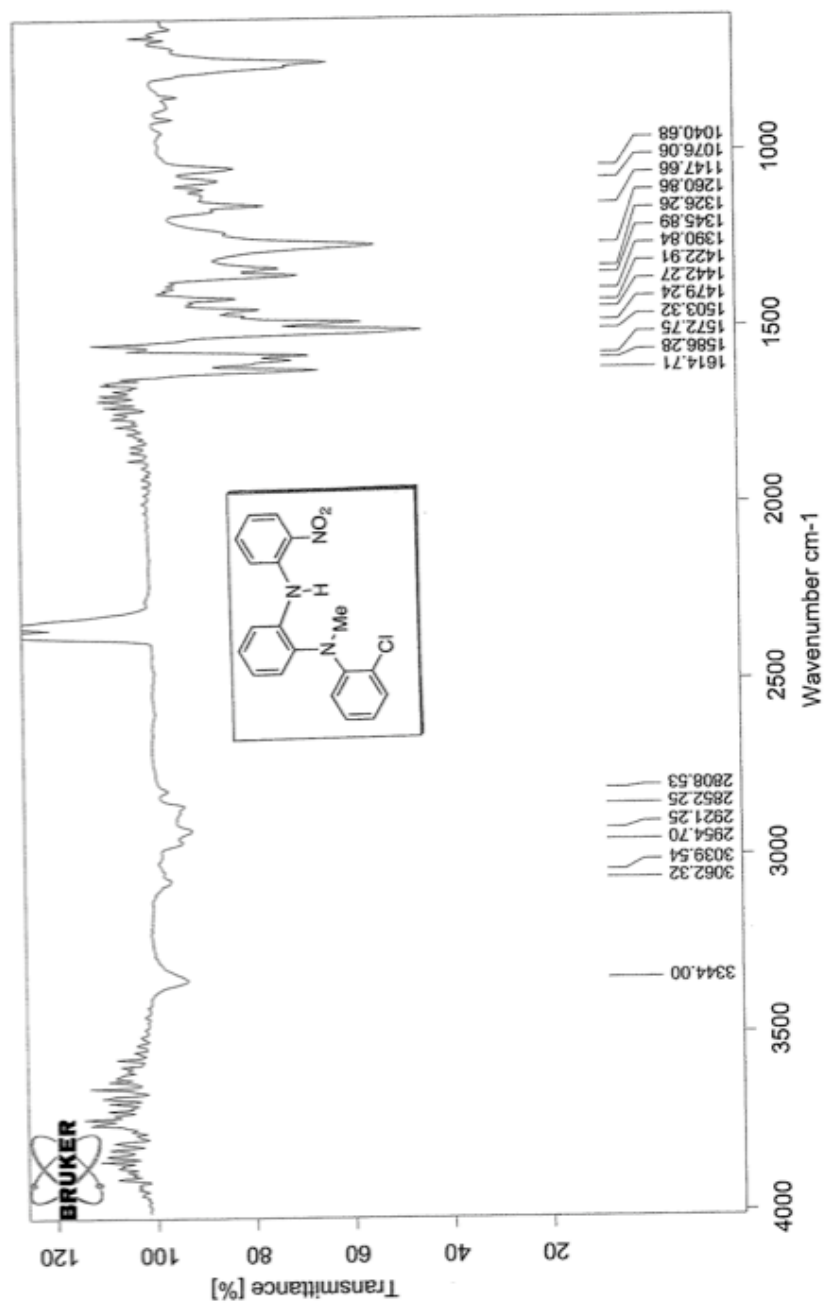








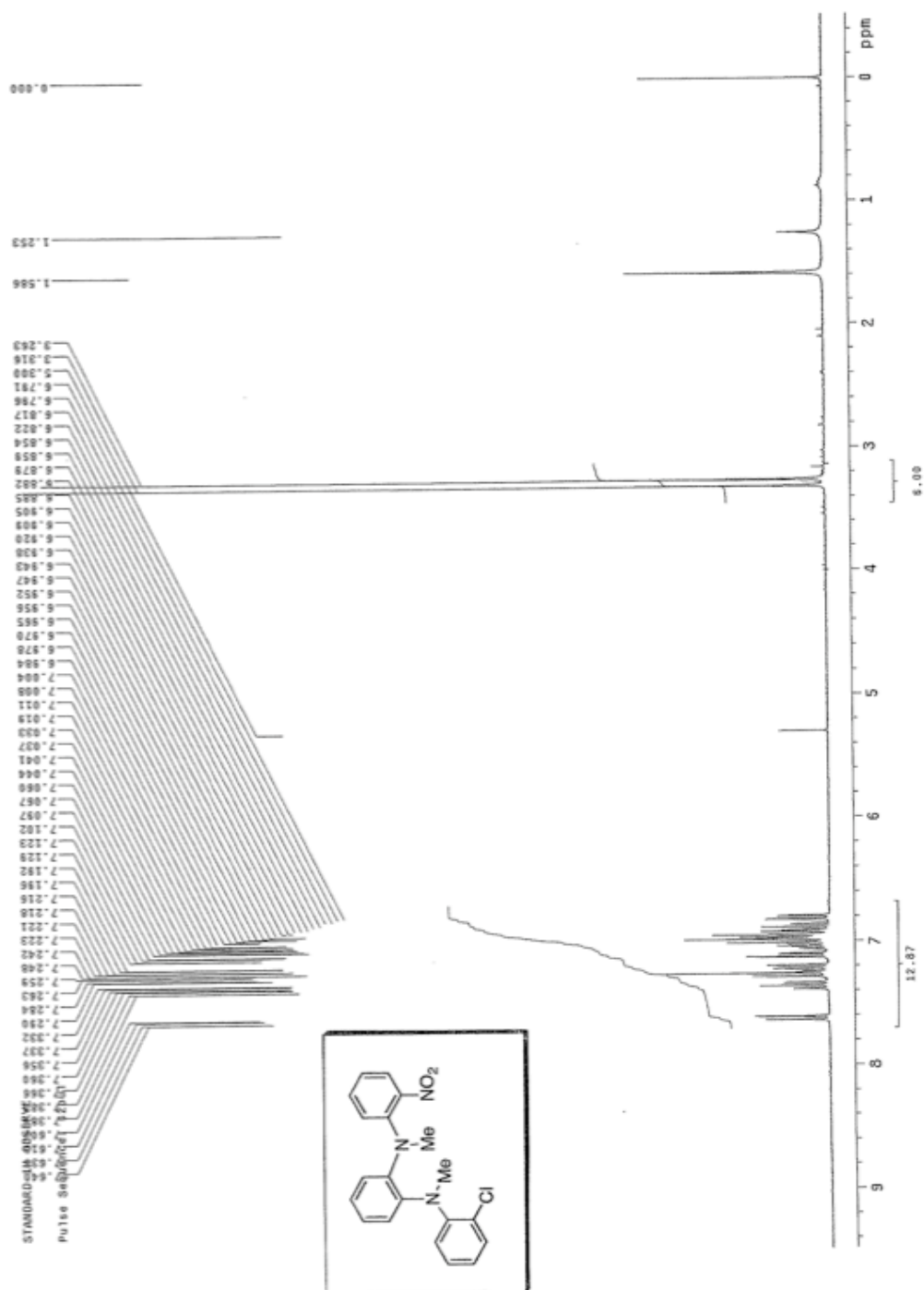


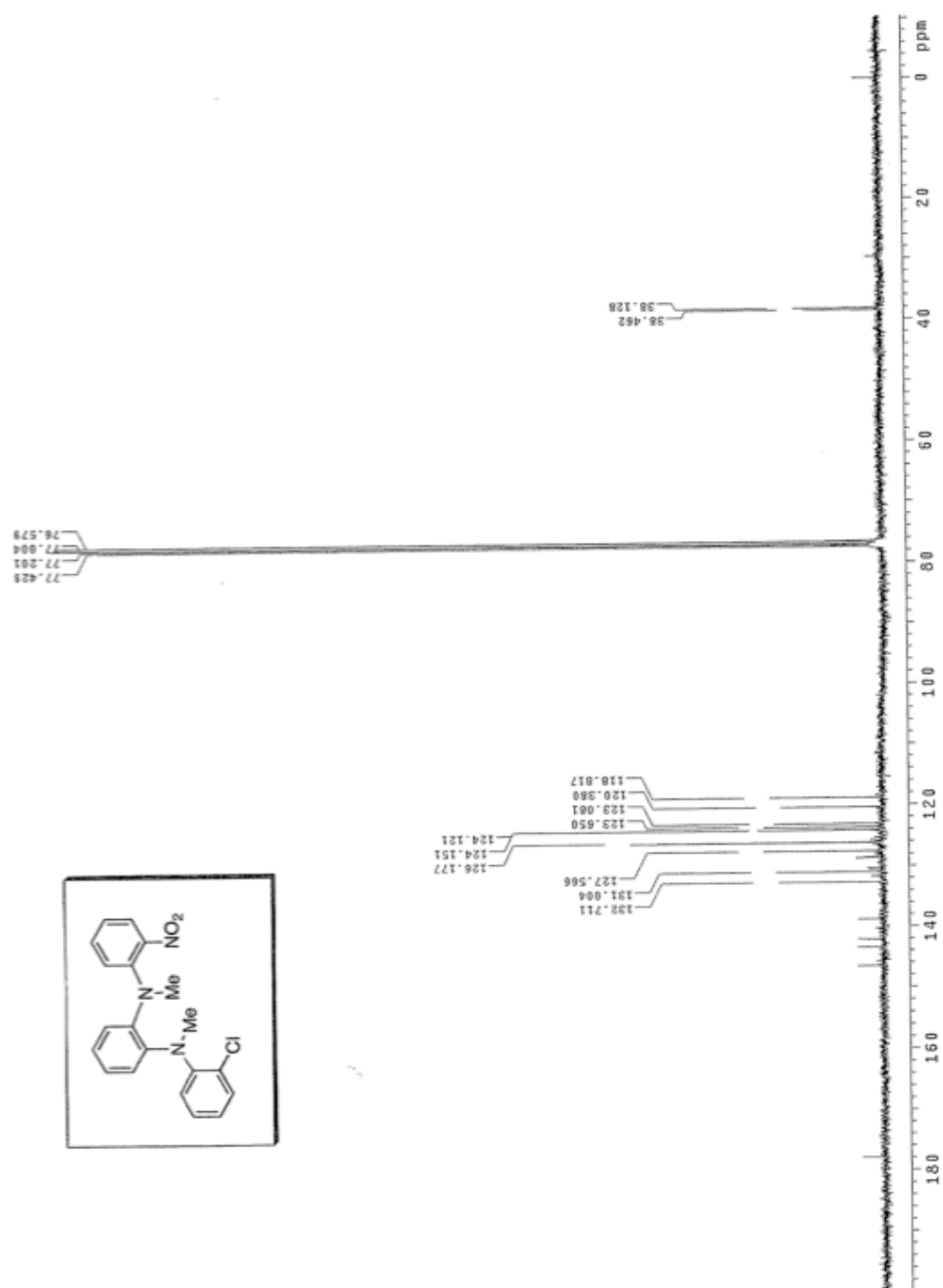


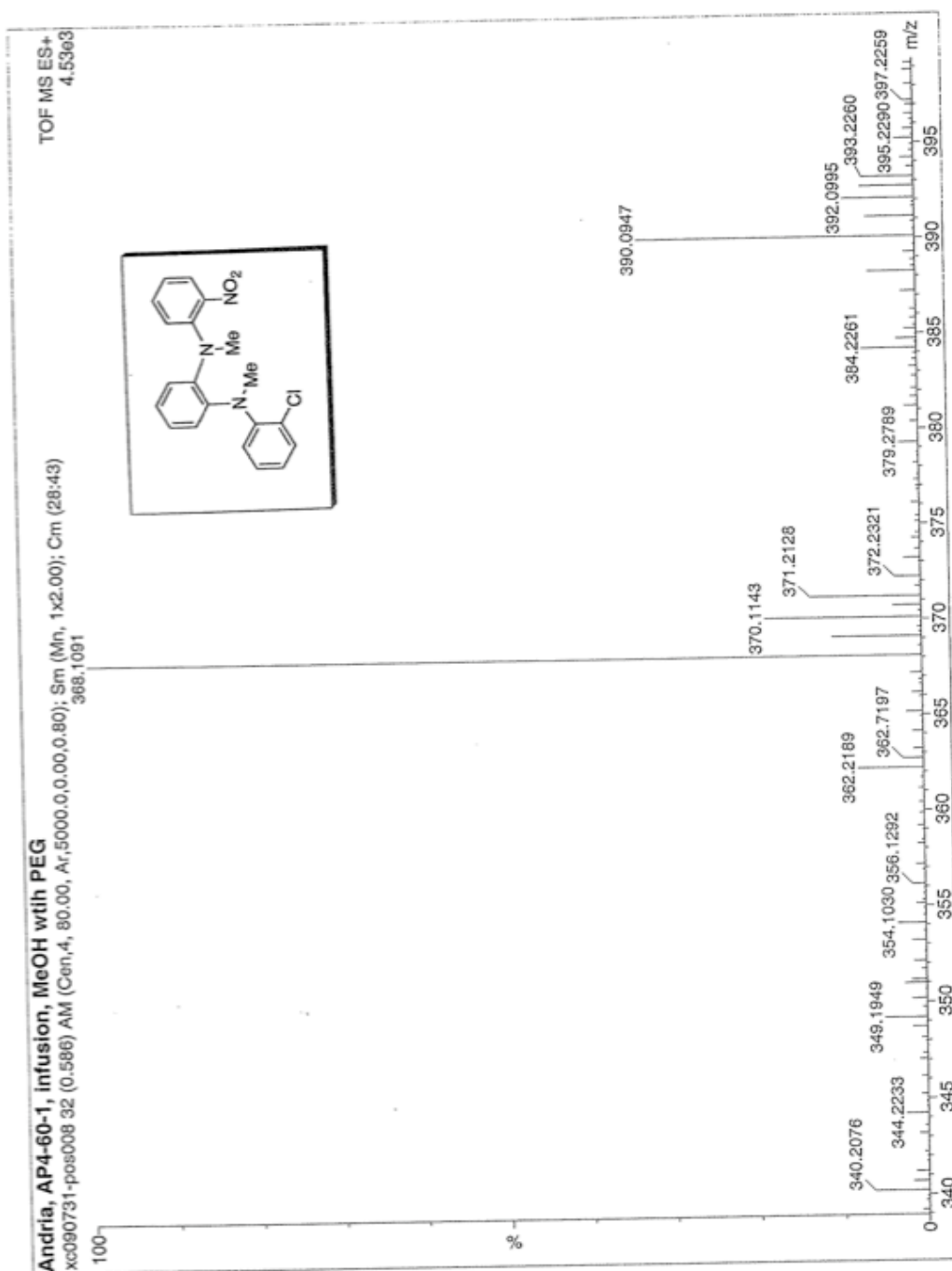
C:\Program Files\OPUS_65\Data\ANDRIA\AP4.0

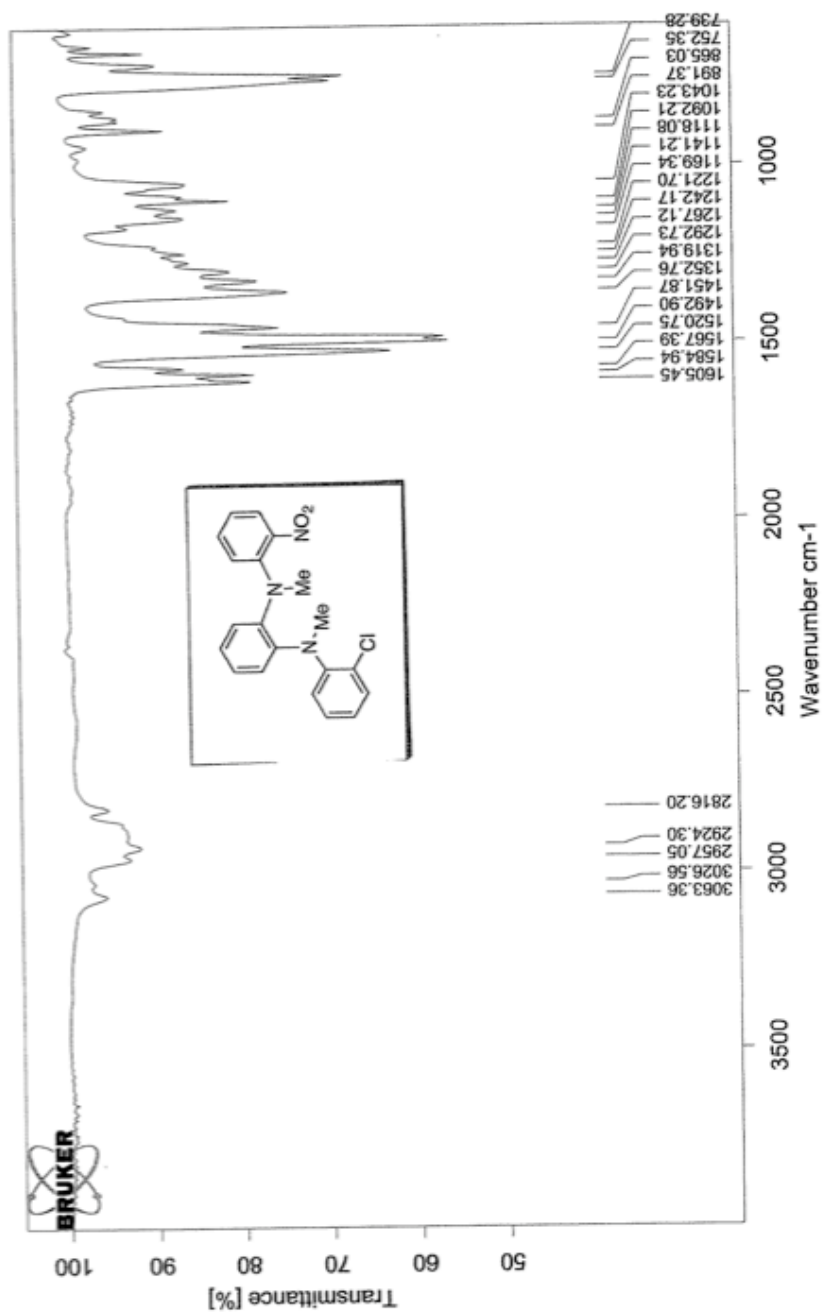
Instrument type and / or accessory

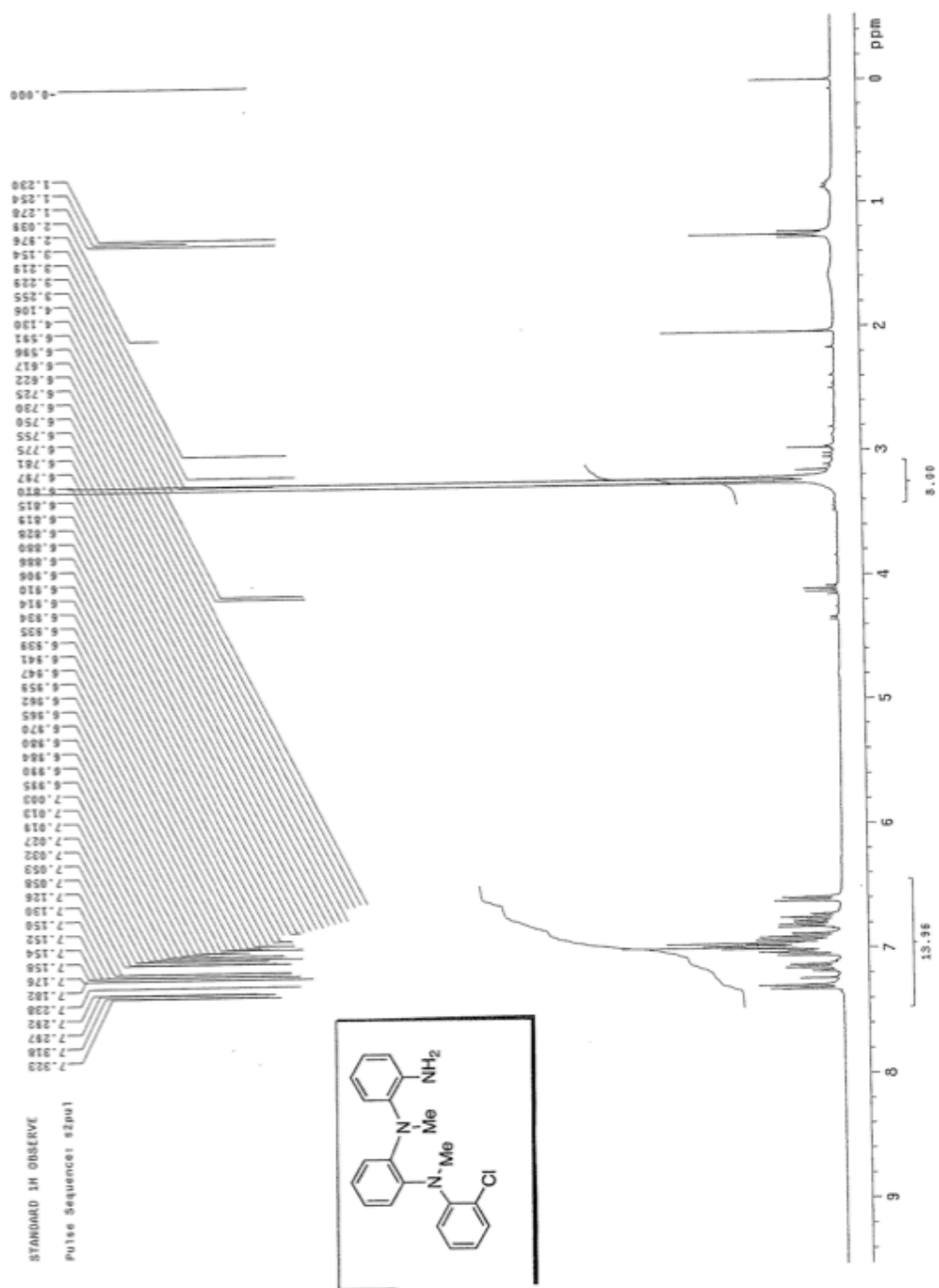
02/06/2010

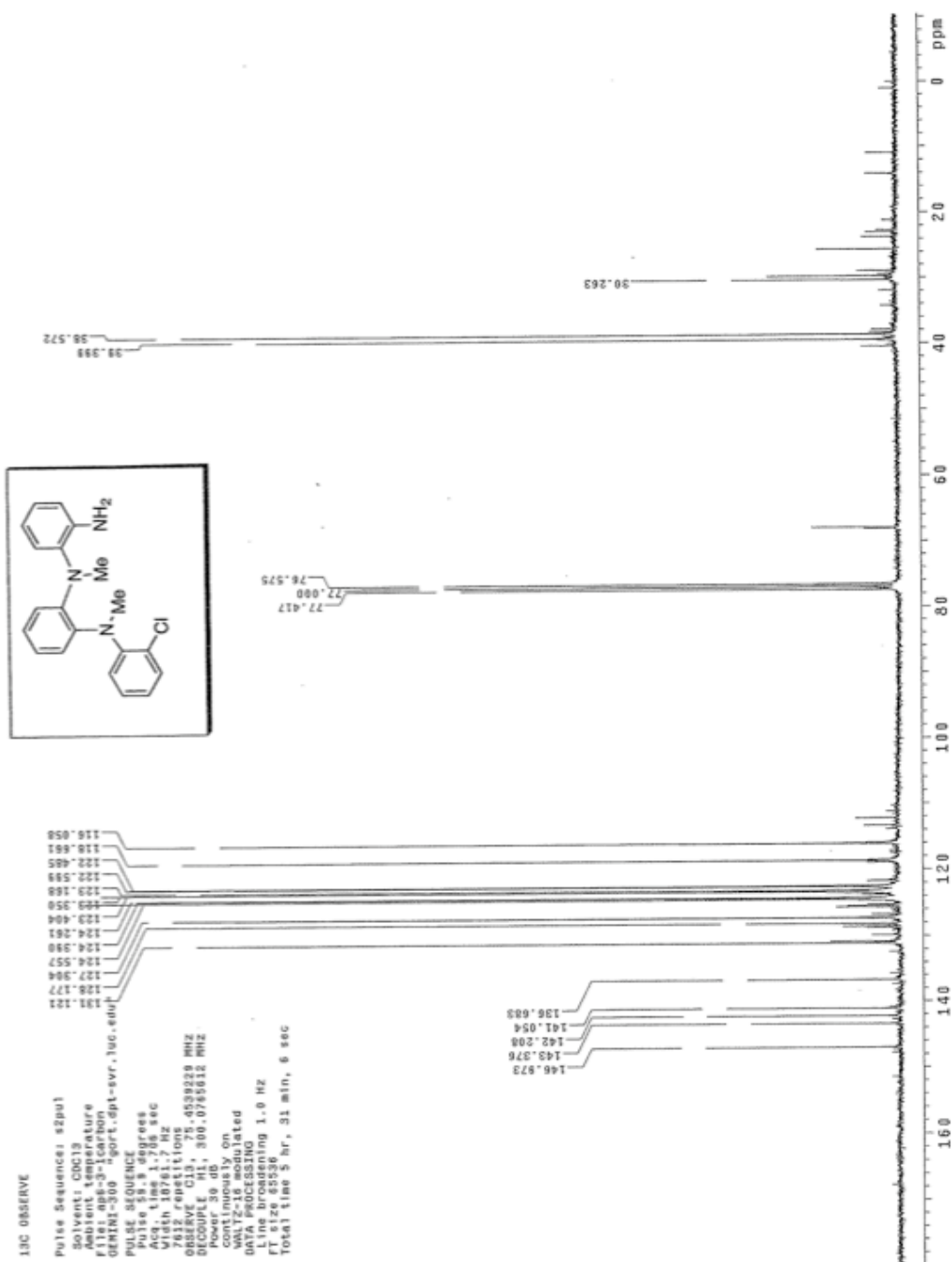


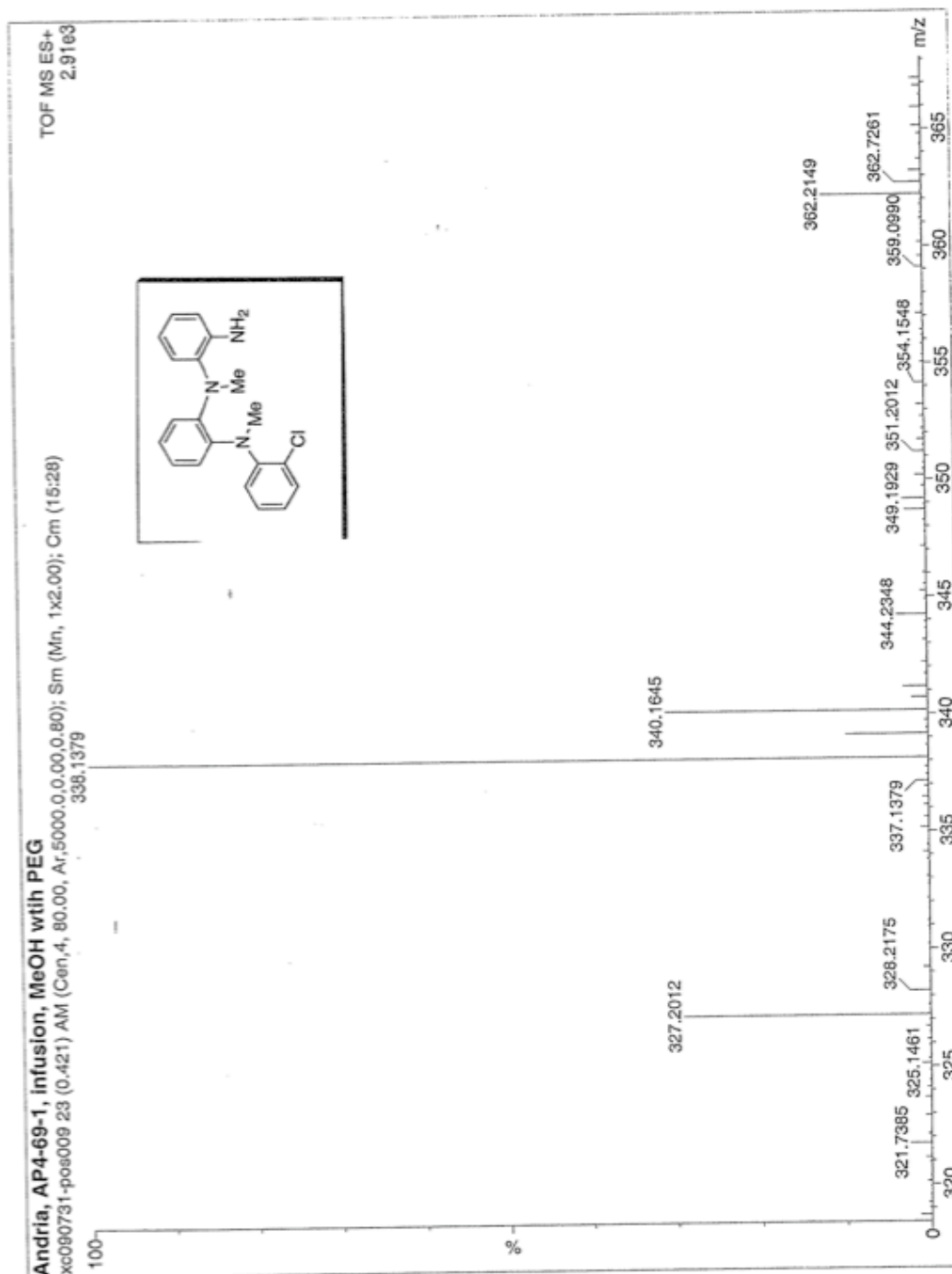


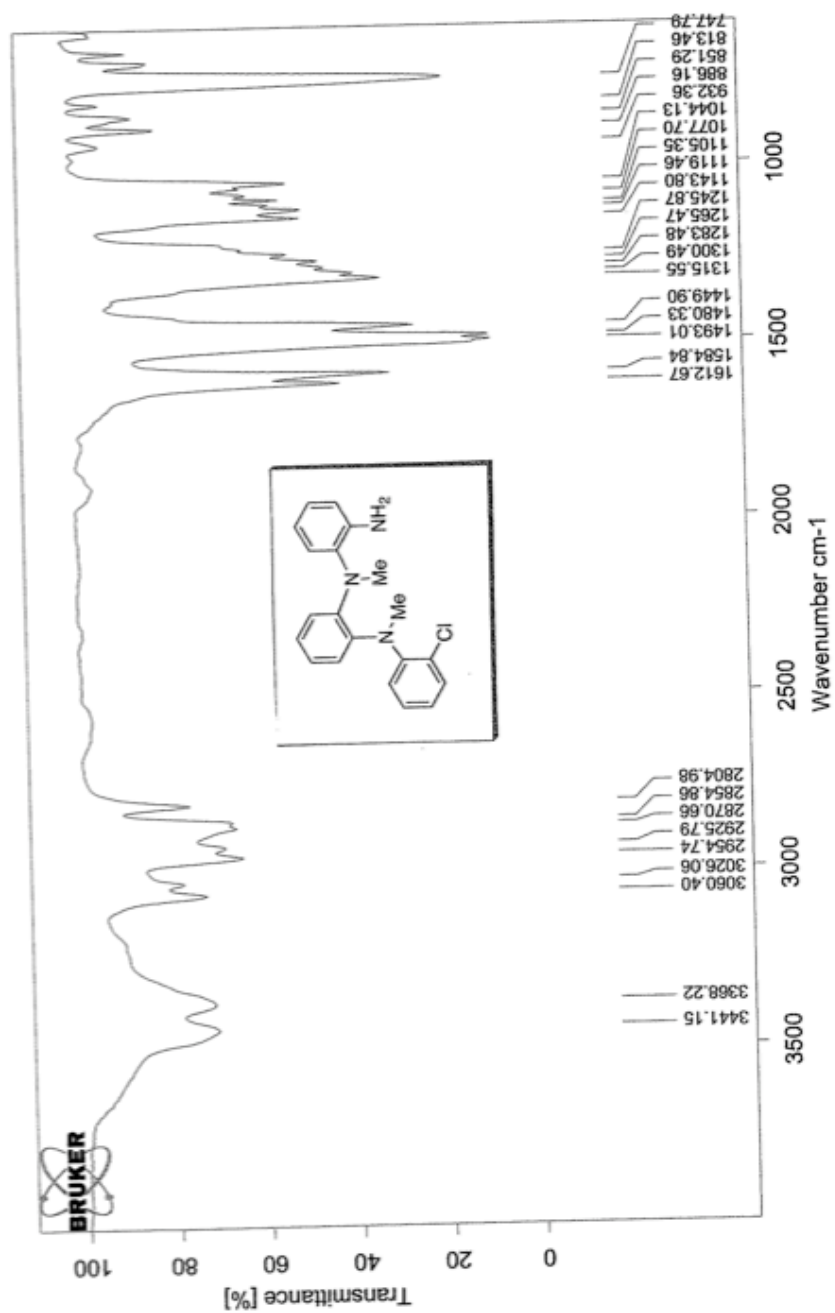


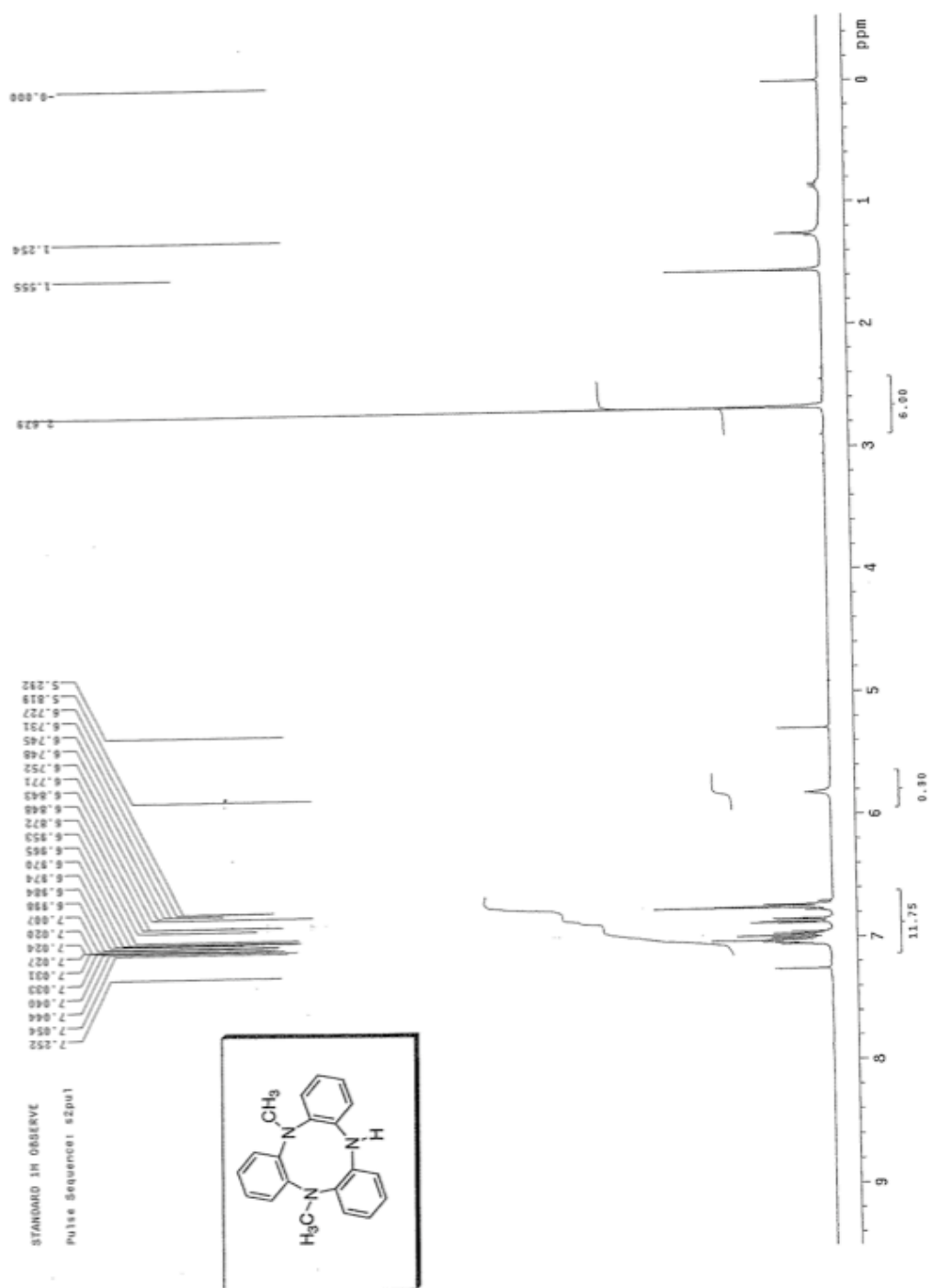


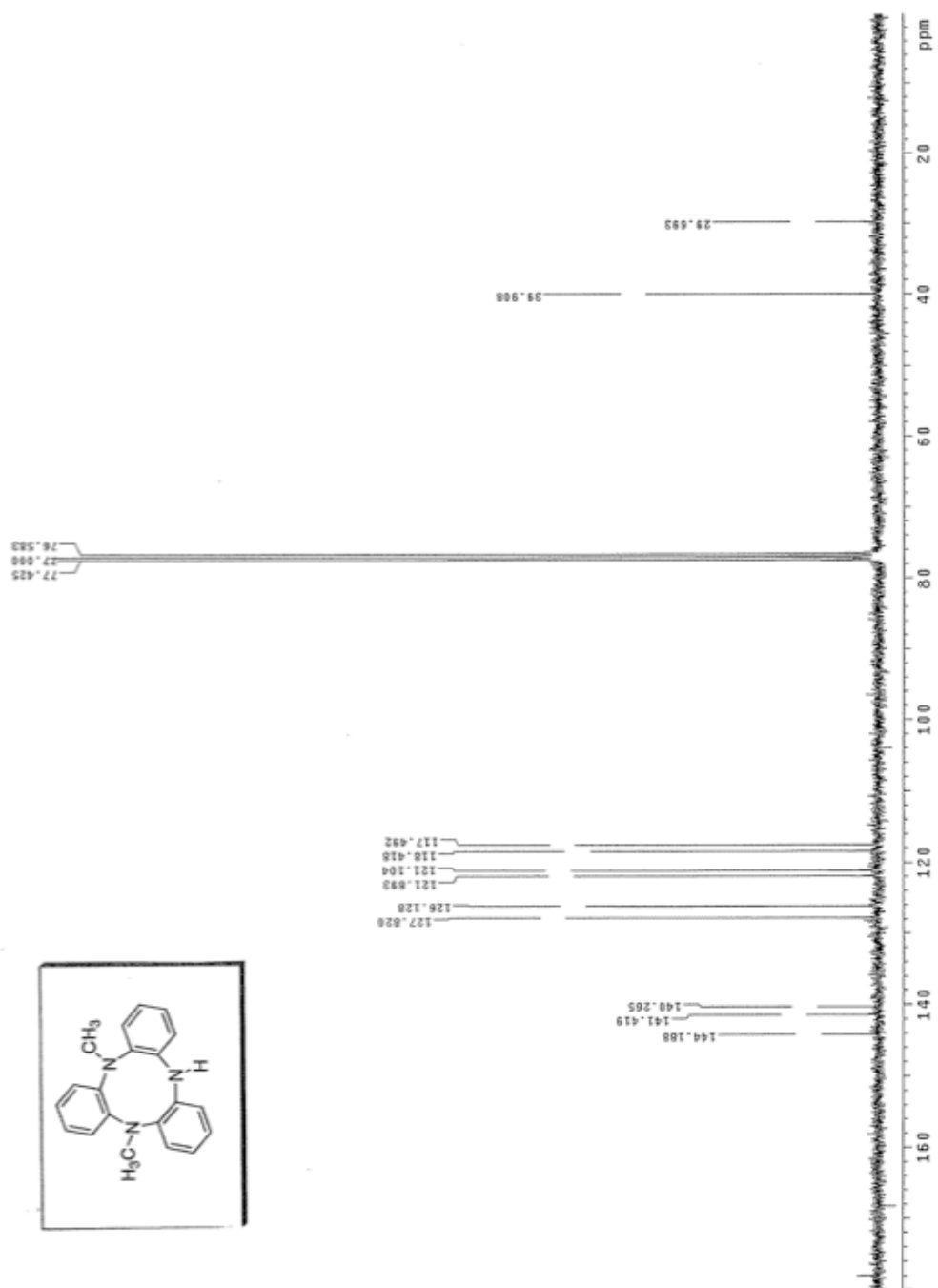


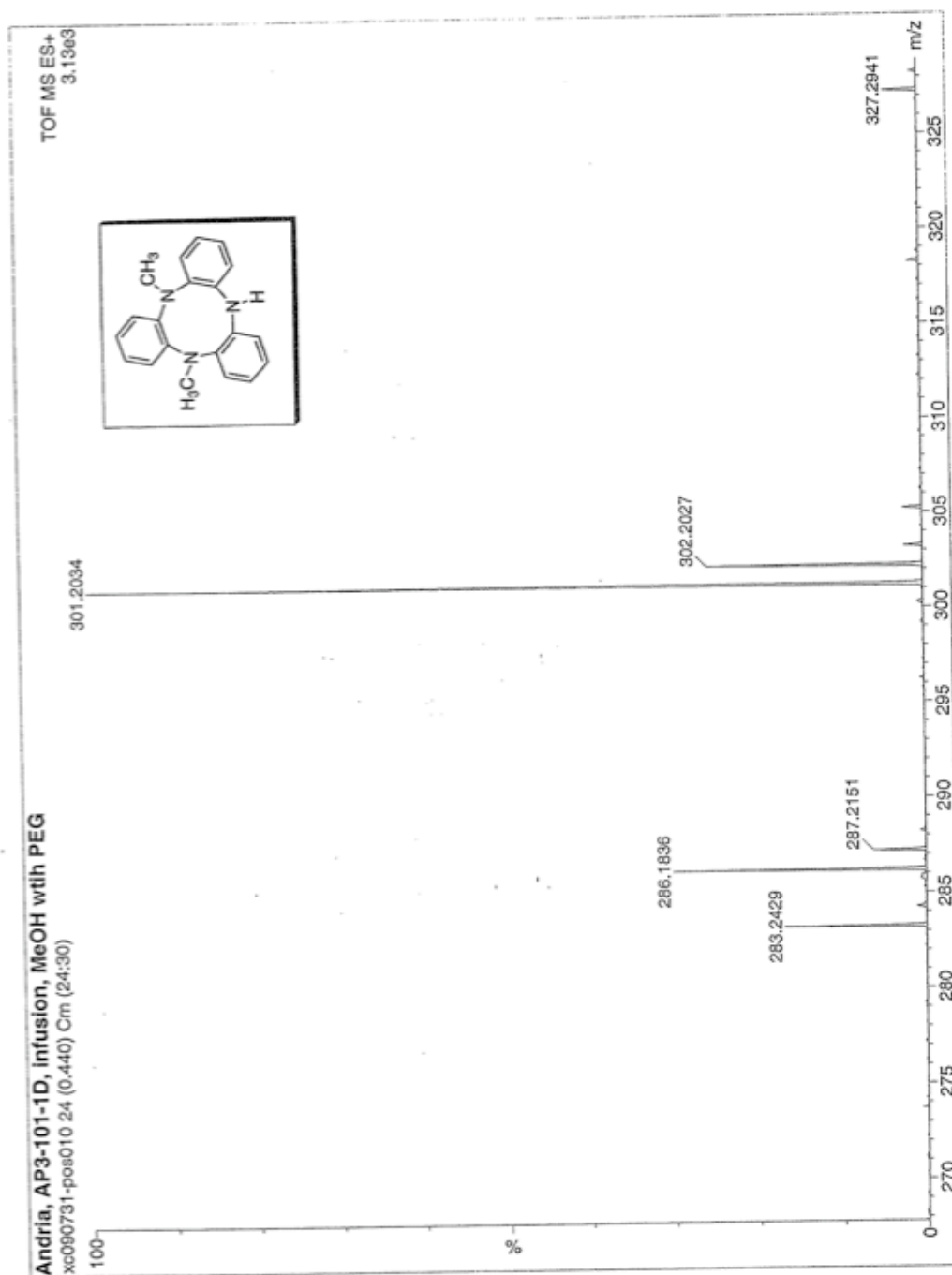


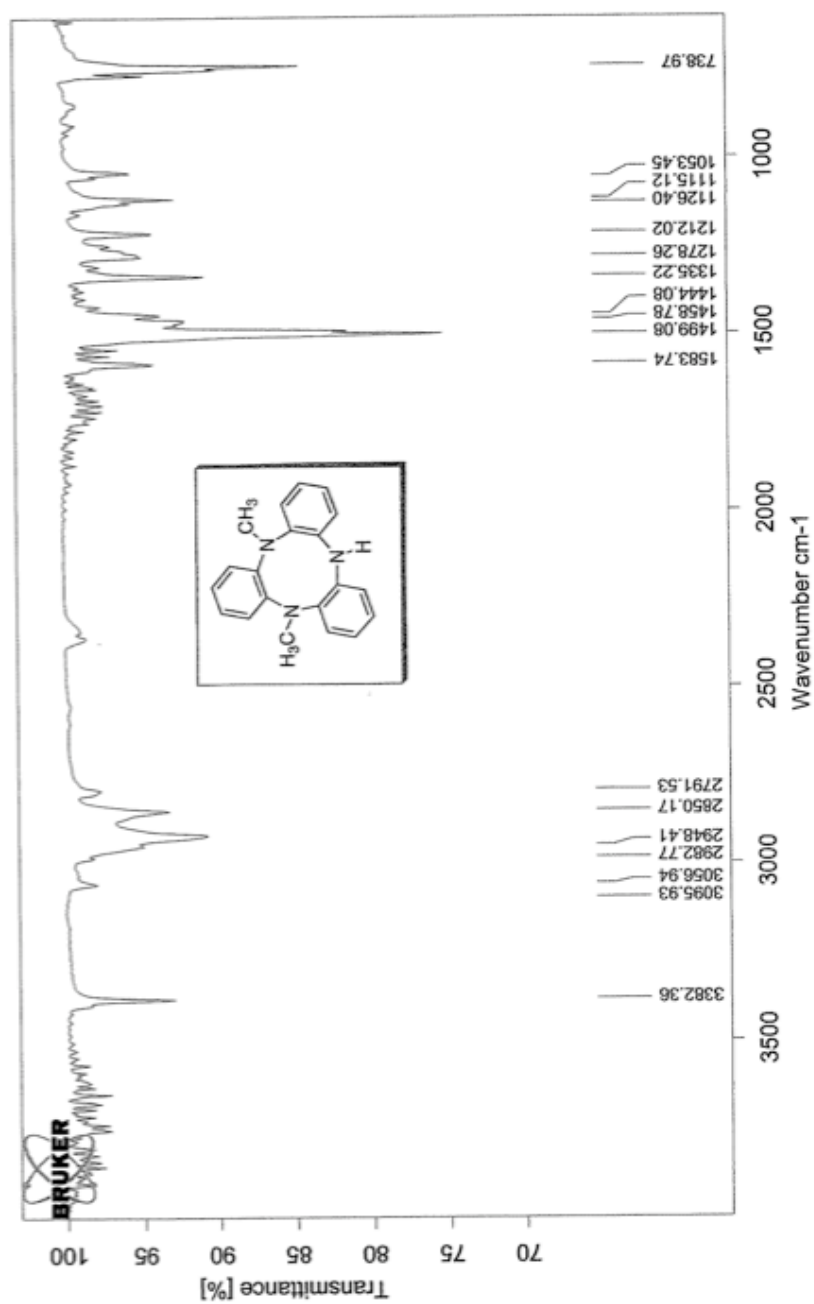


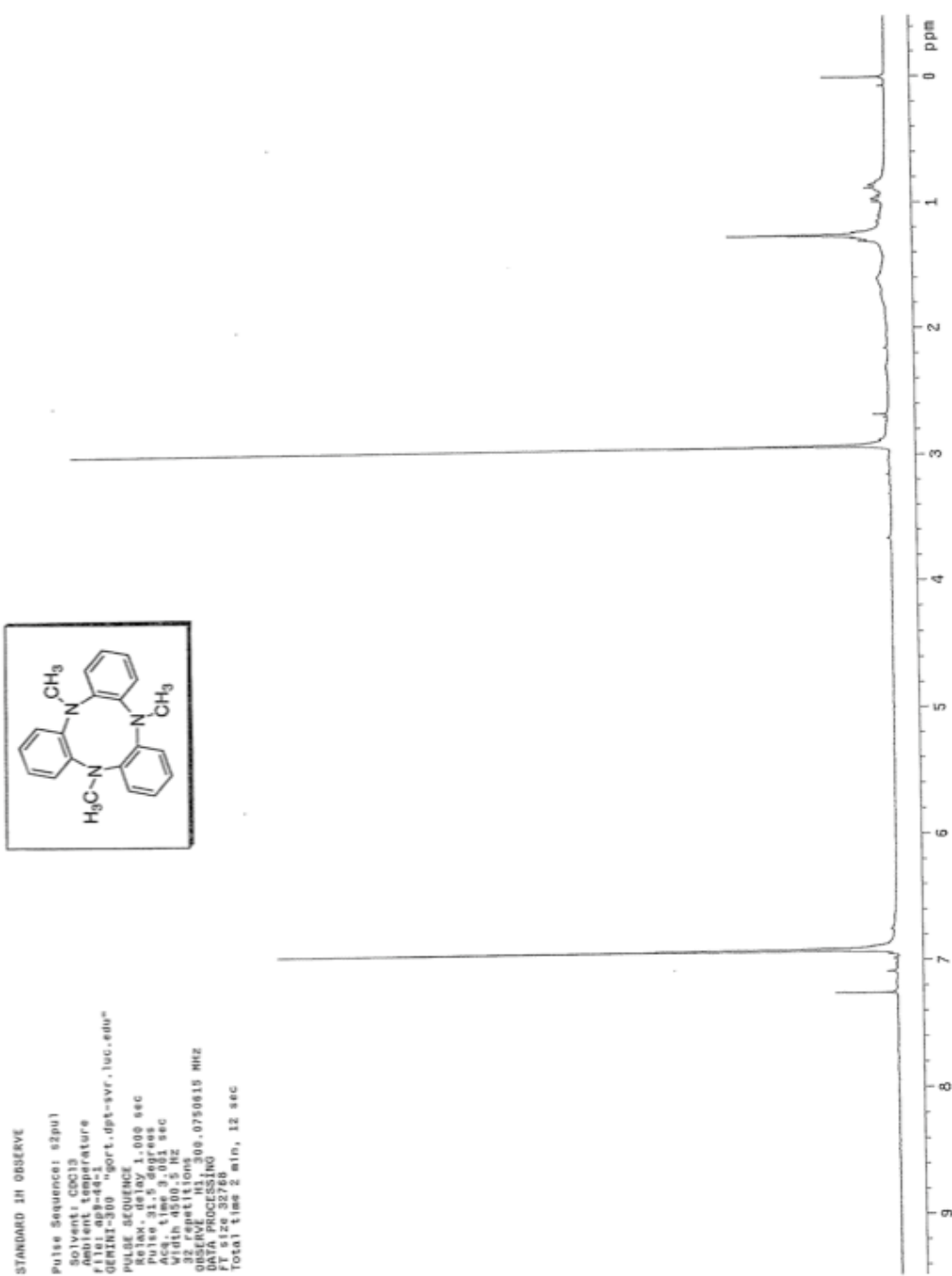






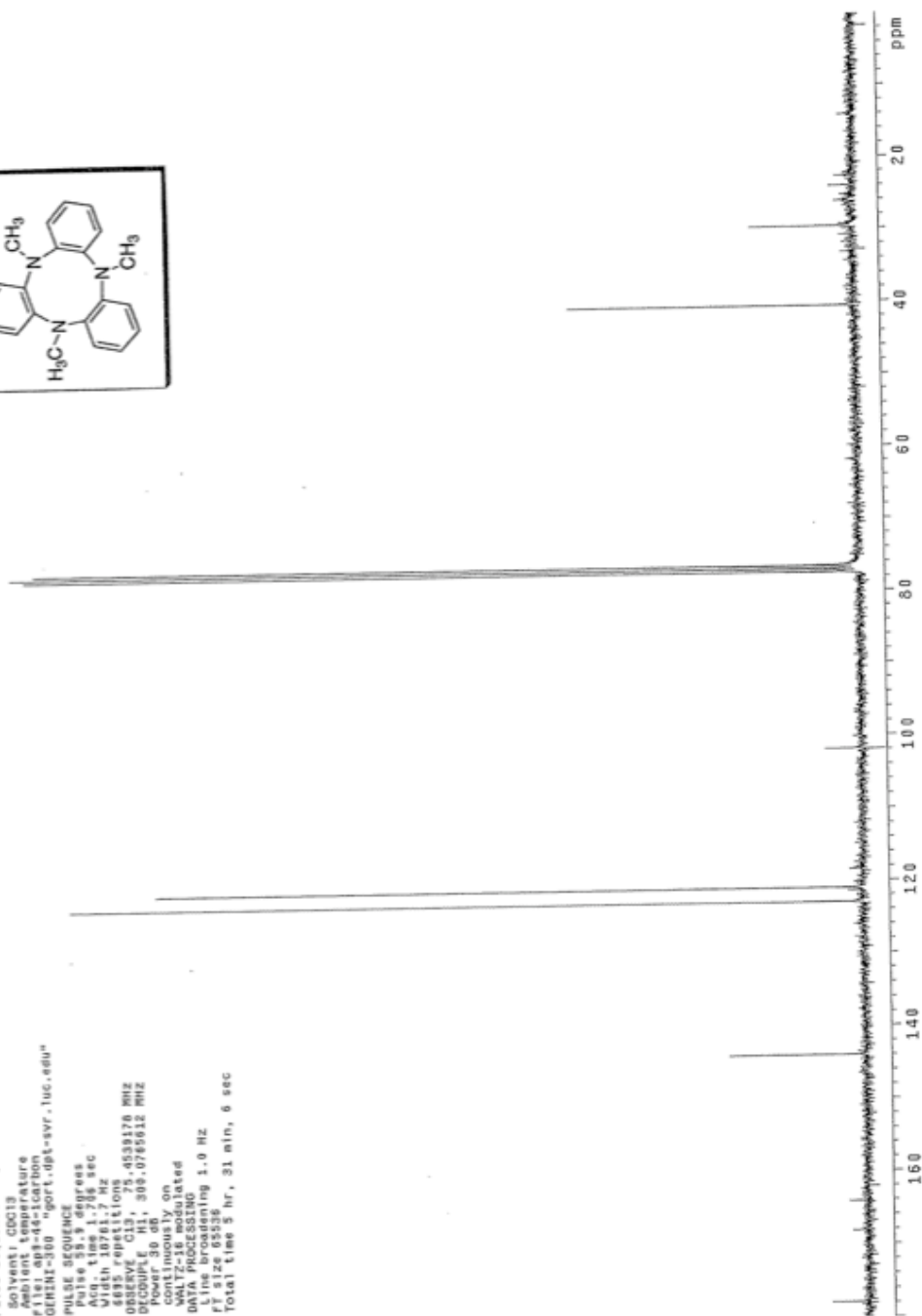
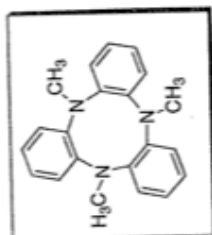




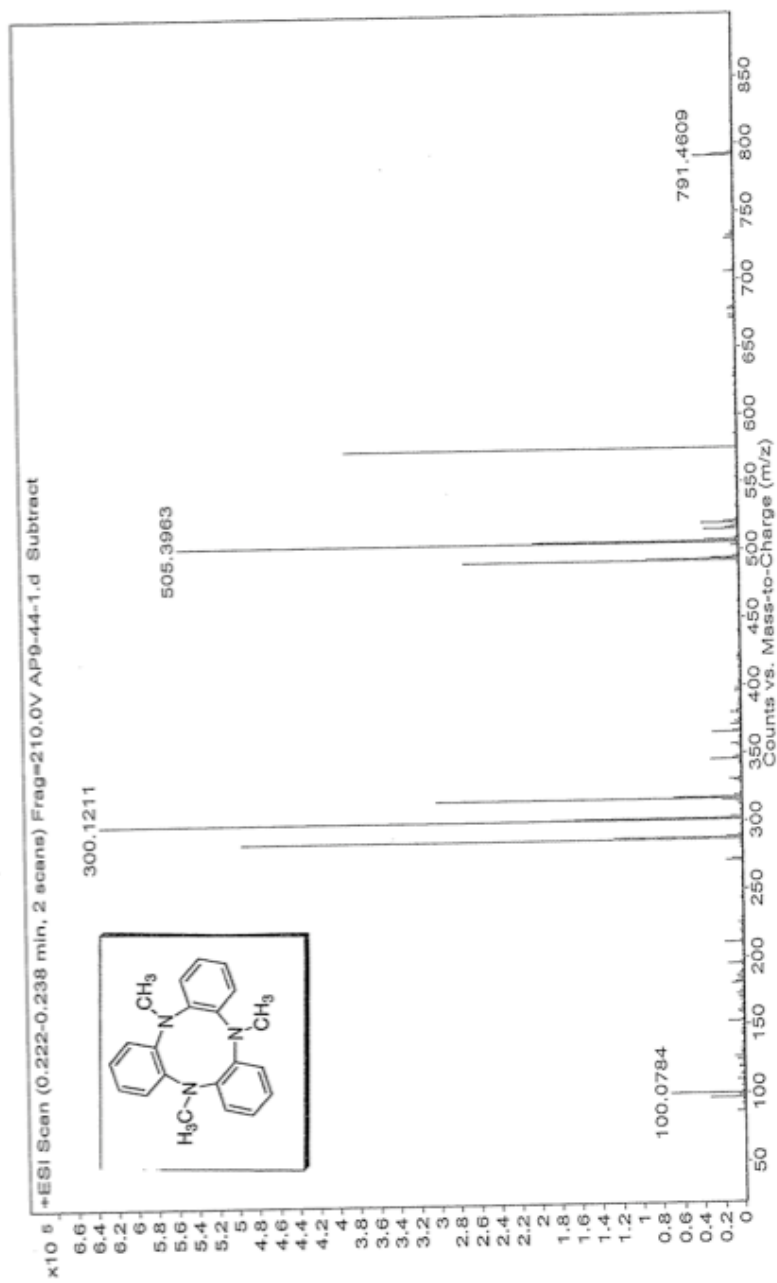


13C OBSERVE

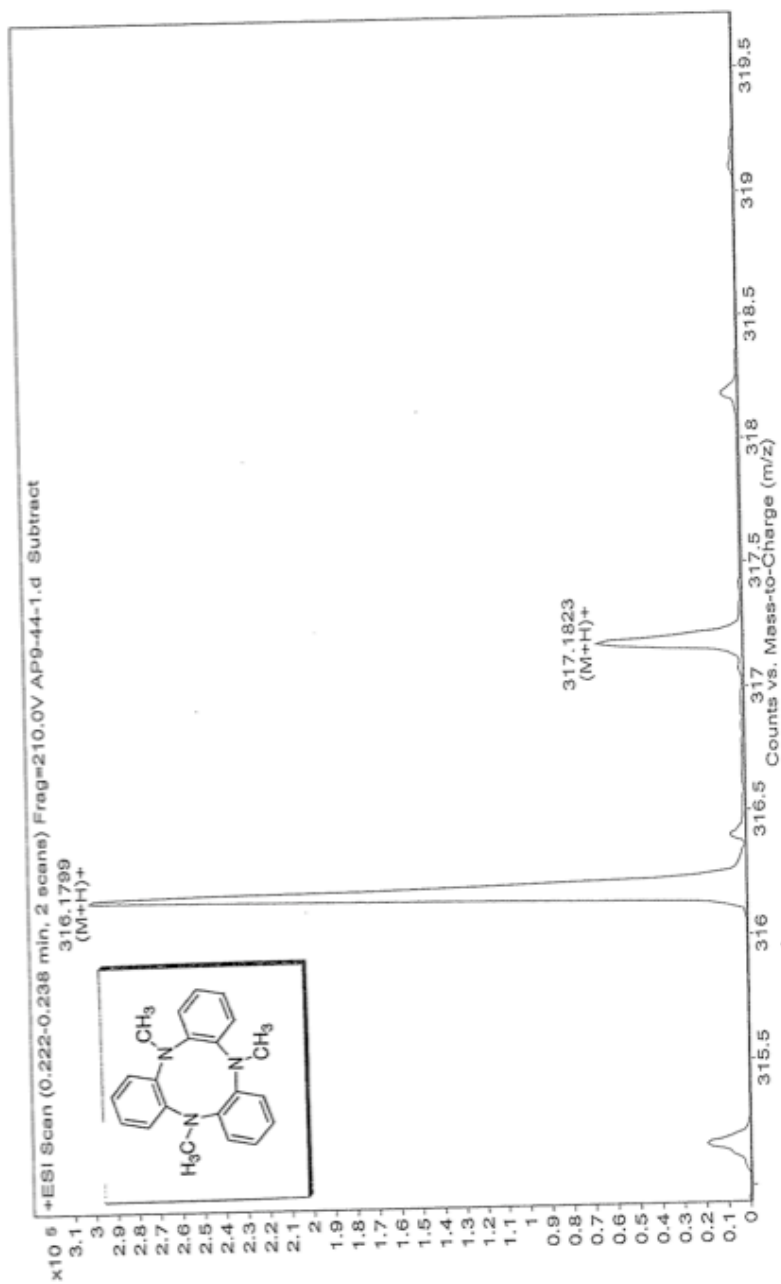
Pulse Sequence: zgpg30
 Solvent: CDCl3
 Acquisition Date: 10/18/05
 File Name: 05-14-11a10m
 GENI: 350 "gort.dpt-svf.tuc.edu"
 PULSE SEQUENCE
 Pulse 53.3 degrees
 Acq. time 1.786 sec
 Width 18761.7 Hz
 OBSERVE C13 75.4539176 MHz
 DECOUPLE H1 300.0745612 MHz
 Power 30 dB
 continuously on
 continuously on
 DATA ACQUISITION
 Line broadening 1.0 Hz
 FT size 65536
 Total time 5 hr, 31 min, 6 sec



Sample Name AP9-44-1
Inj Vol 2
Data Filename AP9-44-1.d
Position InjPosition
ACQ Method
P1-A1
Instrument Name SampleType Comment
ESI_ASL_Pos_03122009
Instrument 1 Sample
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:28:30 AM



Sample Name	AP9-44-1	Position	P1-A1	Instrument Name	Instrument 1	User Name
Inj Vol	2	InjPosition		SampleType	Sample	16M Calibration Status
Data Filename	AP9-44-1.d	ACQ Method	ESI_ASI_Pos_03122009	Comment		Acquired Time
						Success
						6/25/2010 10:28:30 AM

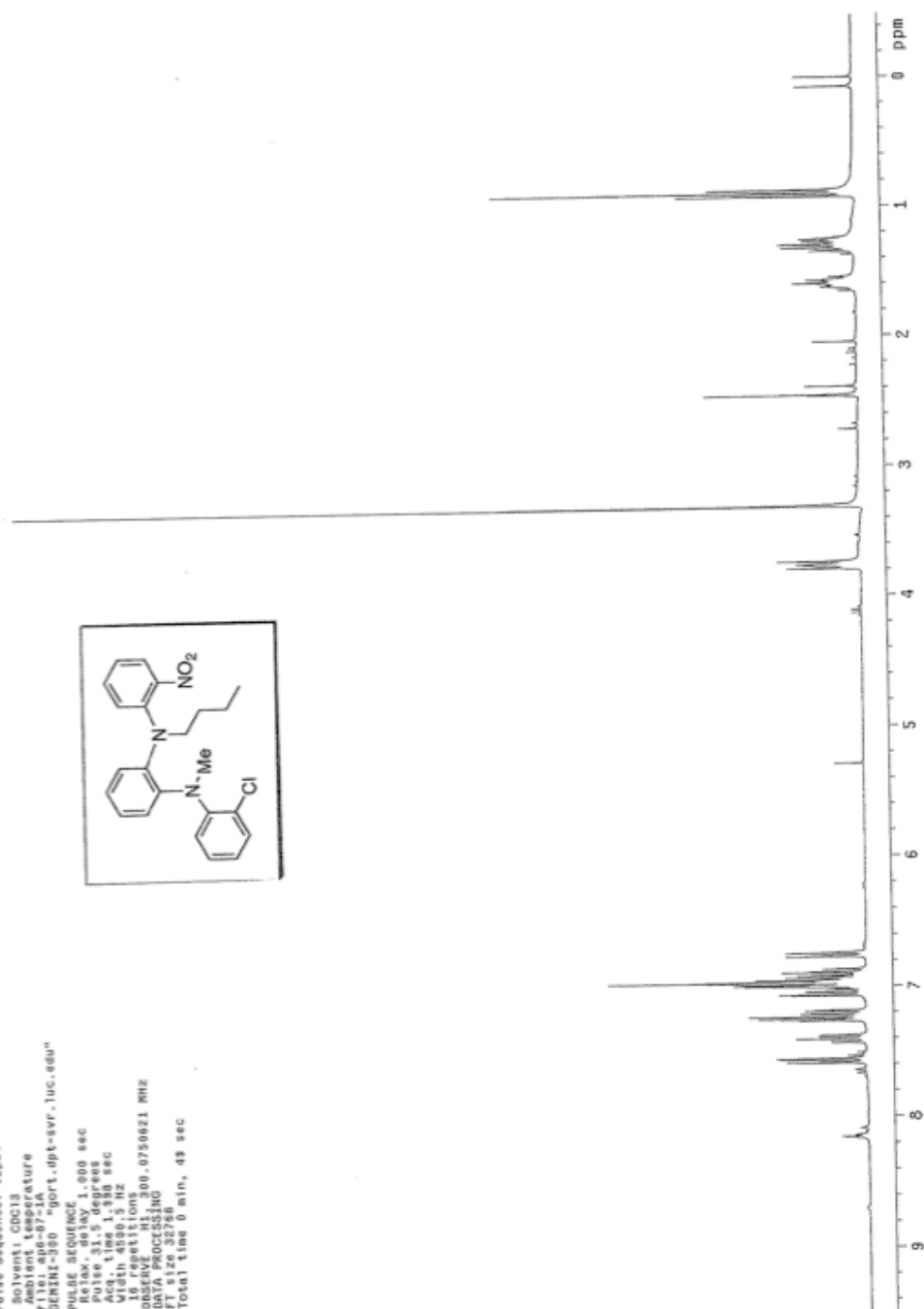
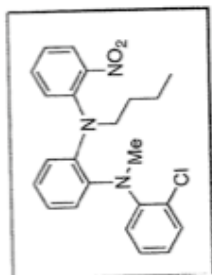


STANDARD IN OBSERVE

```

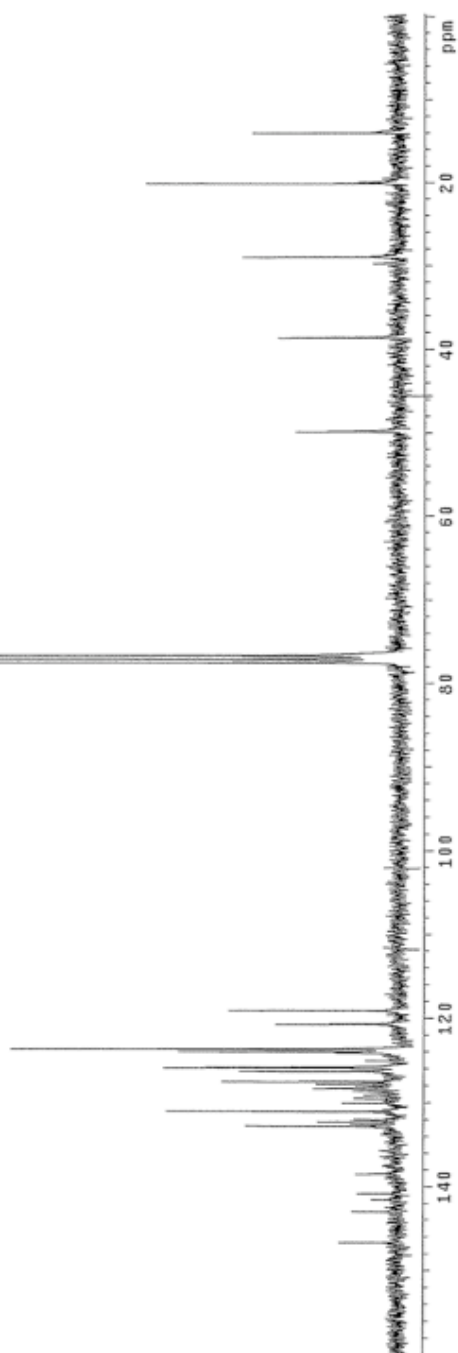
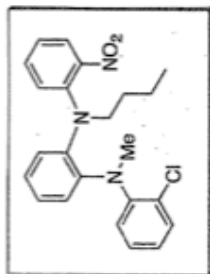
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
C1: sfp-87-1A
C1MSI: 300-jpft-svr_luc.edu
PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 31.5 depress
Acq. time 1.350 sec
Width 4550.5 Hz
10 repetitions
OBSERVE M1, 300.0750621 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec

```

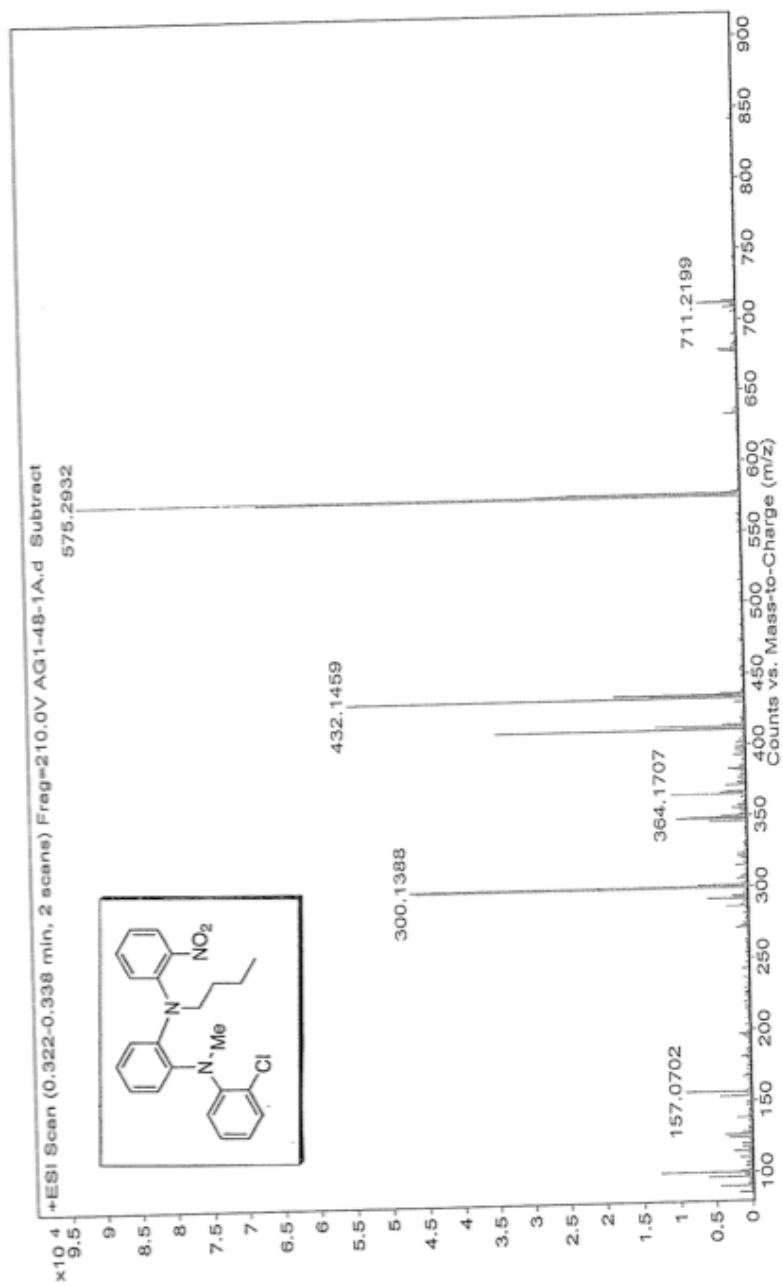


13C OBSERVE

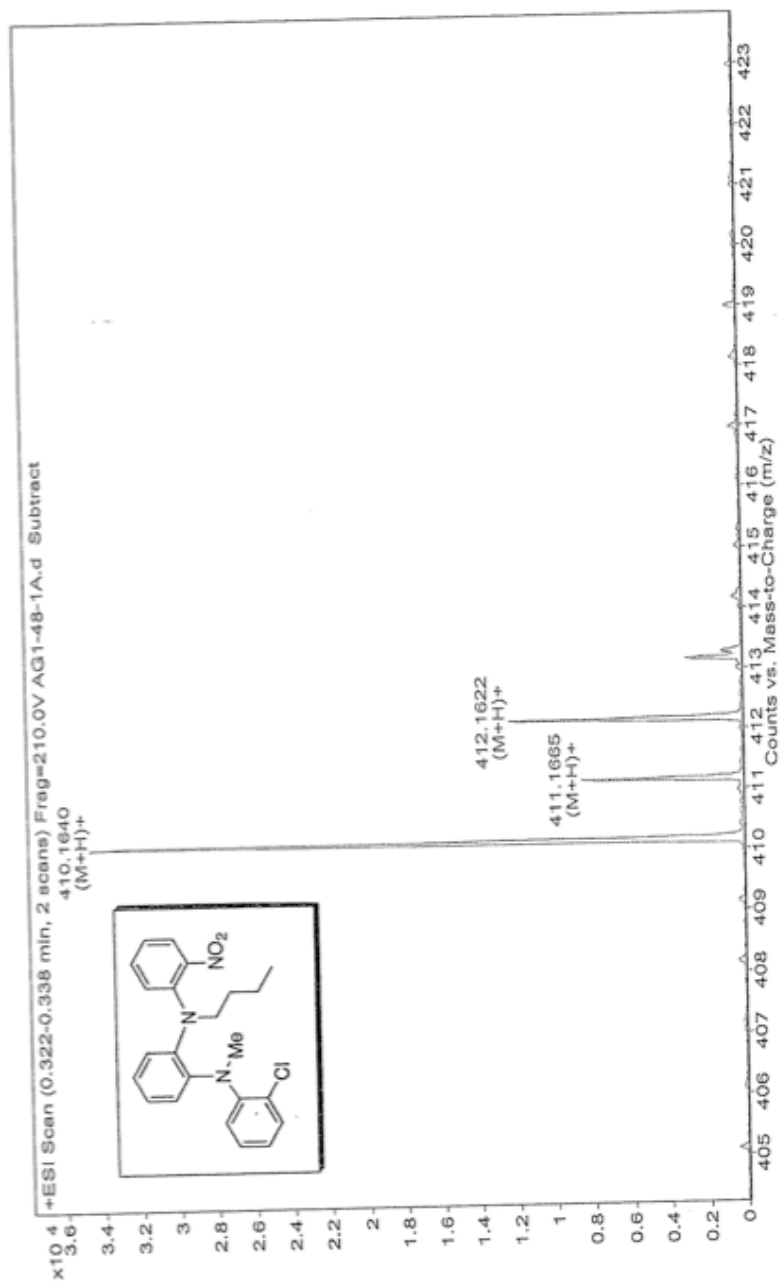
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: AG1-48-1carbon
 GEMIN-385 -gort.cpt-evr.luc.edu
 Pulse sequence
 Channels: 1
 Acq. time 1.766 sec
 Width 18761.7 Hz
 3842 repetitions 459166 MHz
 OBSERVE CH 1
 DECOUPLE M1 380.0765612 MHz
 Power 30 dB
 continuously on
 waltz-16 modulated
 Data processing
 Line broadening 1.0 Hz
 FT size 65536
 Total time 5 hr. 31 min. 6 sec

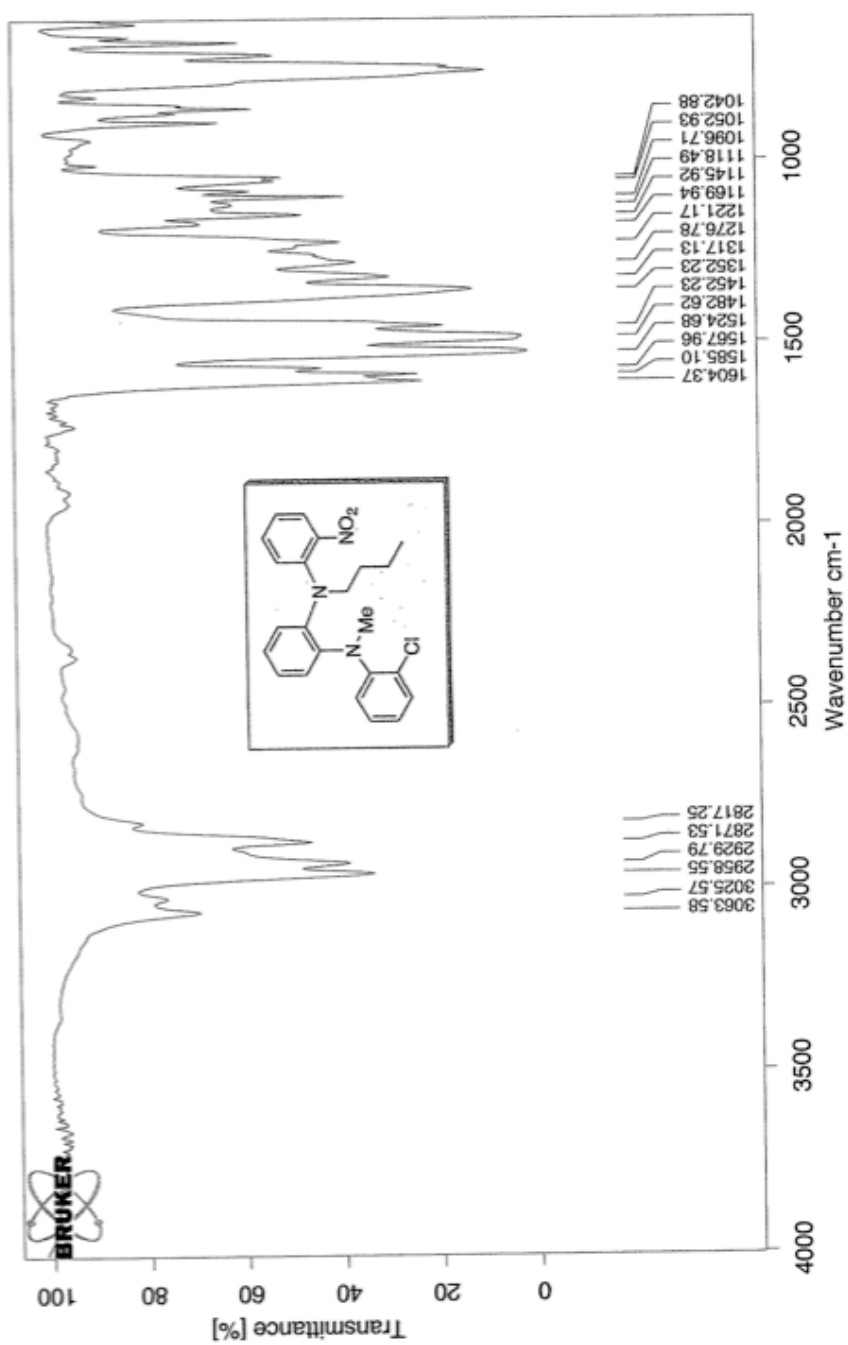


Sample Name	AG1-48-1A	Position	PL-A2	Instrument Name	Instrument 1	User Name	Success
Inj Vol	2	InjPosition	ESL_ASL_Pos_03122009	SampleType	Sample	IRM Calibration Status	6/25/2010 10:31:07 AM
Data Filename	AG1-48-1A.d	ACQ Method		Comment		Acquired Time	



Sample Name AGI-48-1A
Inj Vol 2
Data Filename AGI-48-1A.d
Position InjPosition
ACQ Method
P1-A2
ESL_ASL_Pos_03122009 Comment
Instrument Name Sample
Instrument 1
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:31:07 AM



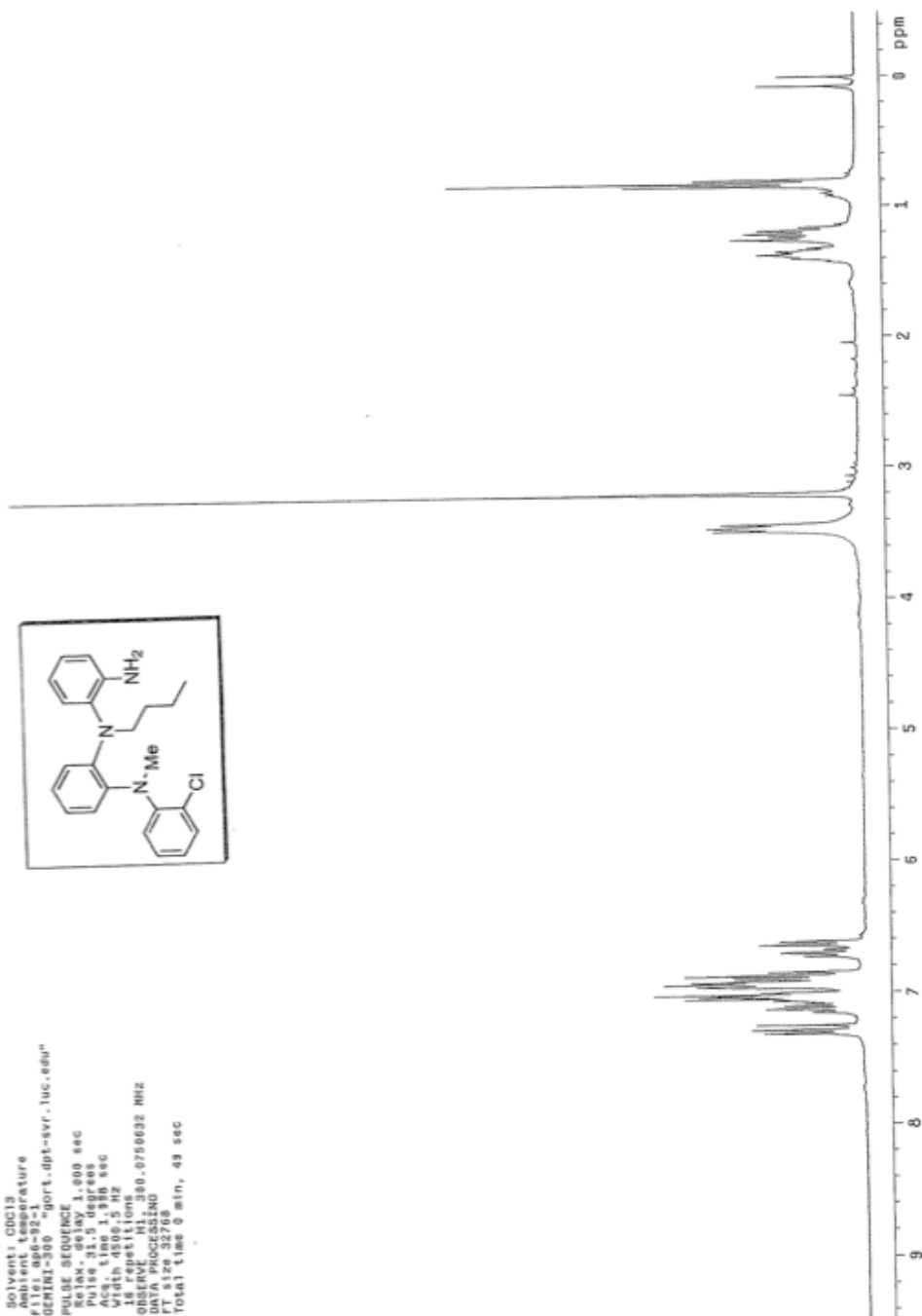
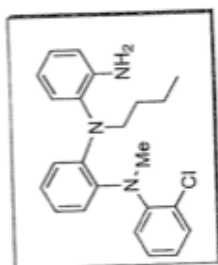


STANDARD 1H OBSERVE

Pulse Sequence: s2p01
Solvent: CDCl3
Acquire Date: 06/11/01
Acquire Time: 10:00:00
File: ap6-92-1
GEMRI-300 "gort-dpt-svr-luc.edu"

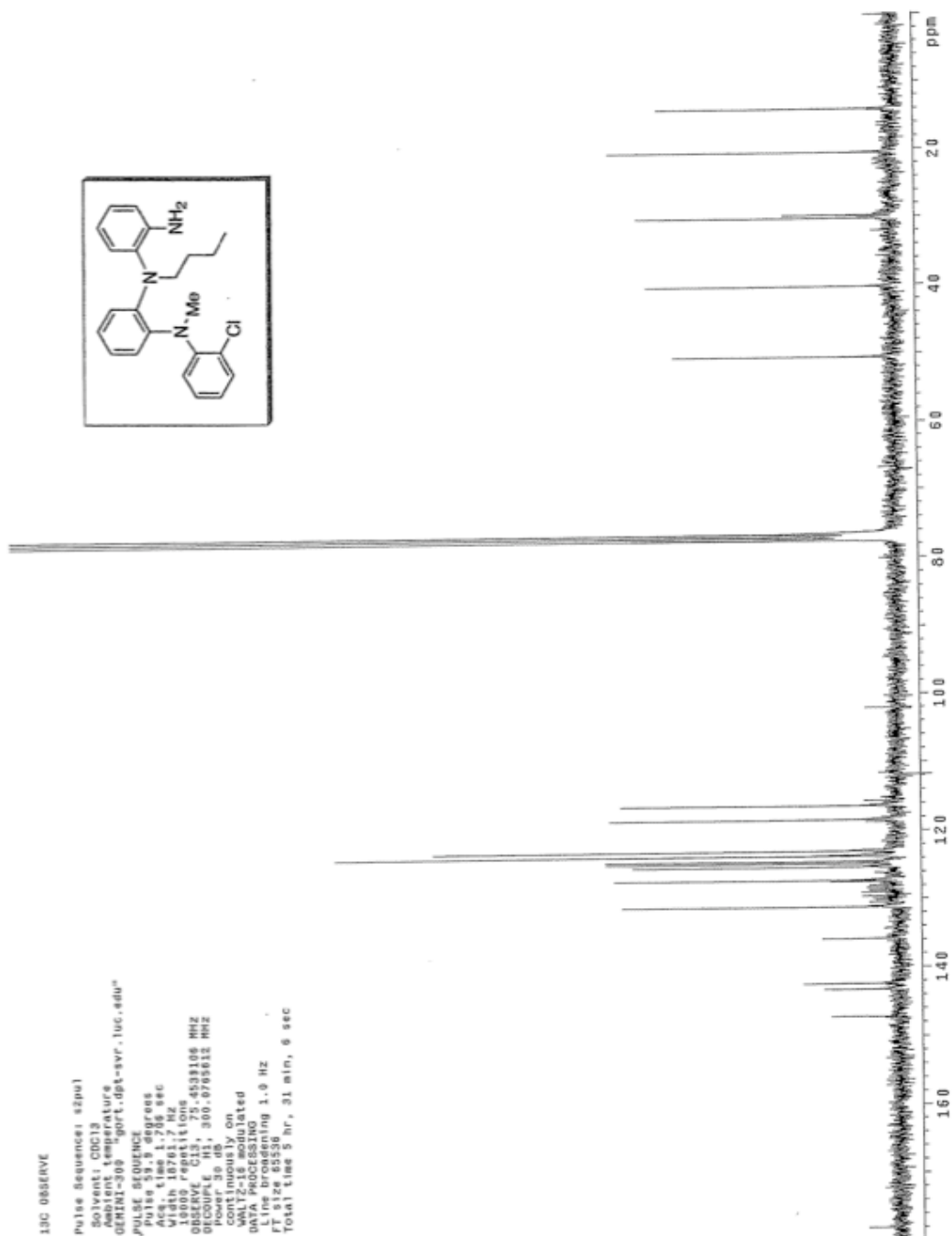
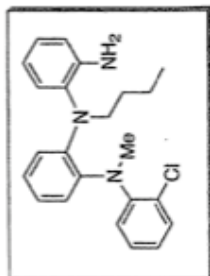
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. 10.000 sec
Width 4500.5 Hz
18 repetitions

OBSERVE M1, 300.0750032 MHz
DATA PROCESSING
F2 300.0750032 MHz
Total time 0 min, 49 sec

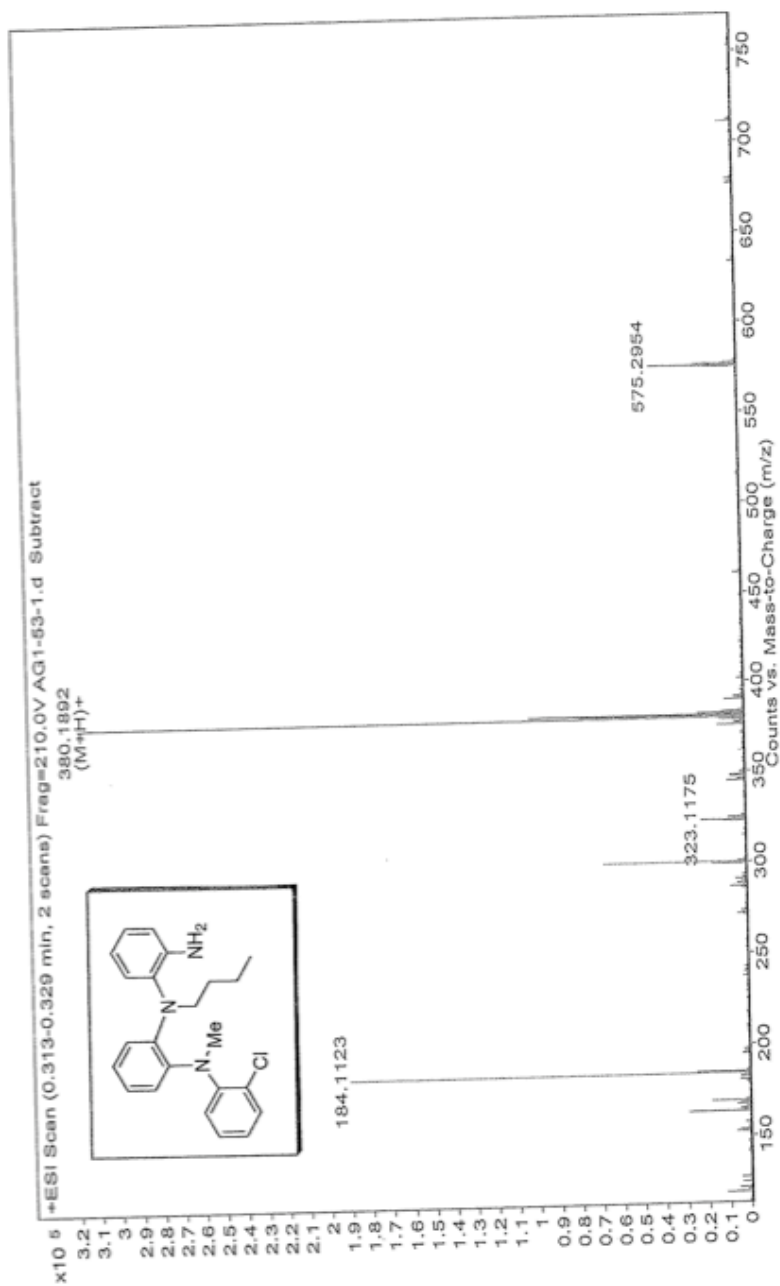


¹³C OBSERVE

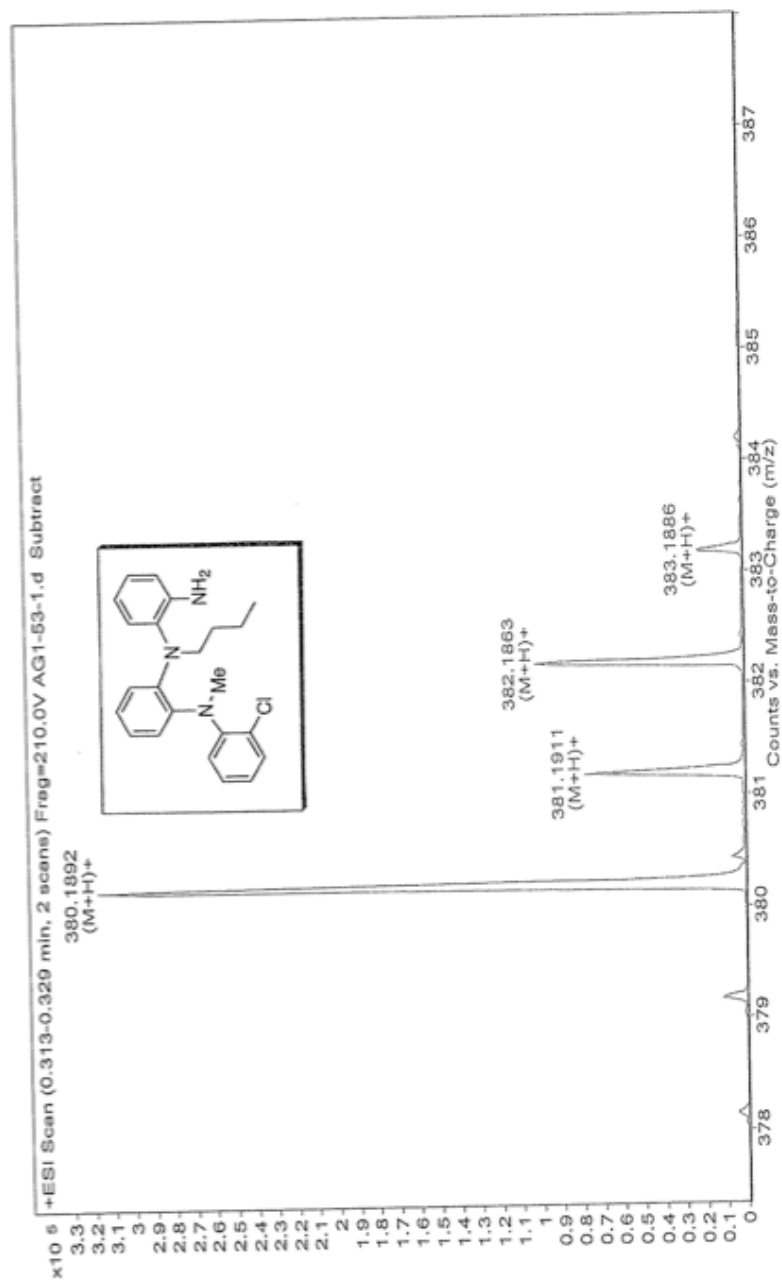
Pulse Sequence: szpu1
 Solvent: CDCl3
 Ambient temperature
 GENI-300 "gfort.svr.luc.edu"
 PULSE SEQUENCE
 zgpg30
 Pulse 51.3 degrees
 Width 18.75 sec
 Width 18761.7 Hz
 16000 repetitions
 OBSERVE C13, 75.4539106 MHz
 DECOUPLE H1, 300.0705612 MHz
 Locking on continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 65536
 Total time 5 hr, 31 min, 6 sec

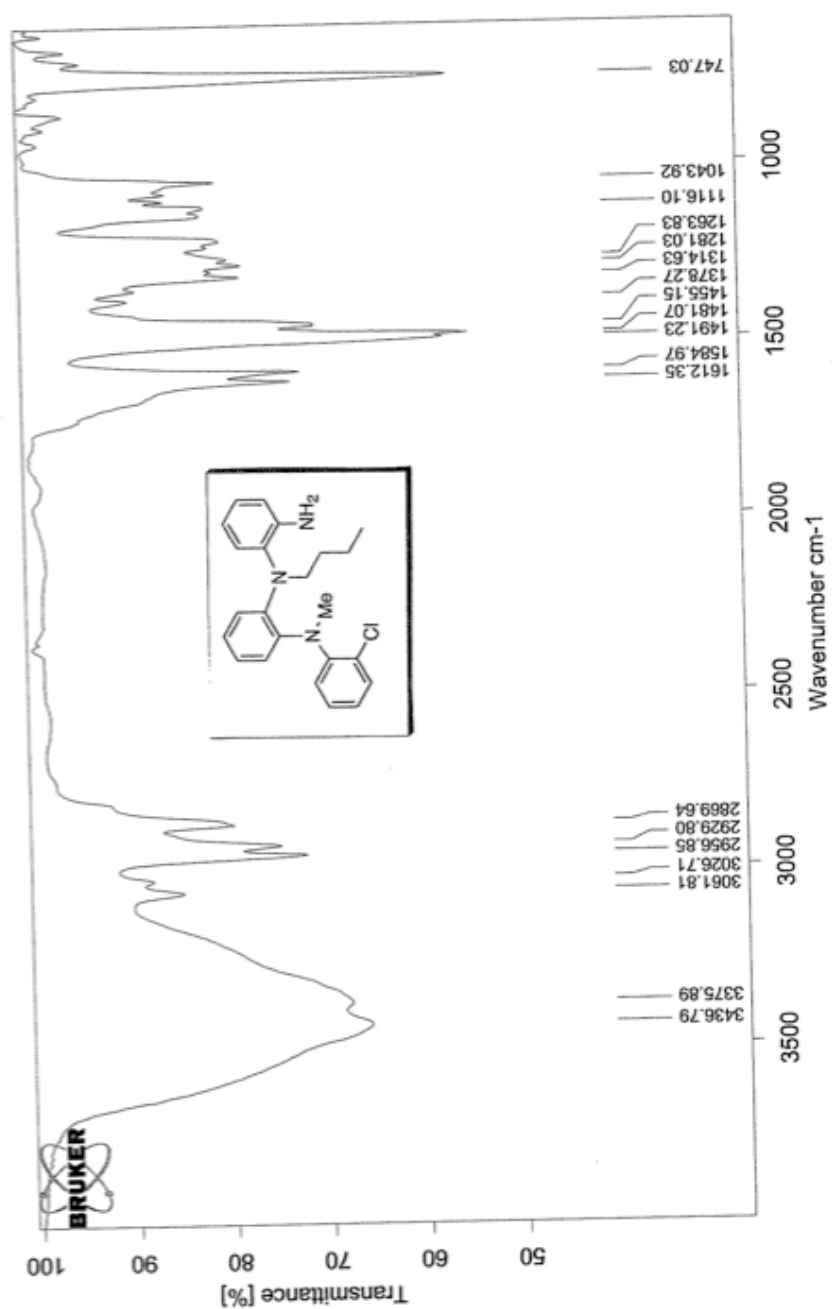


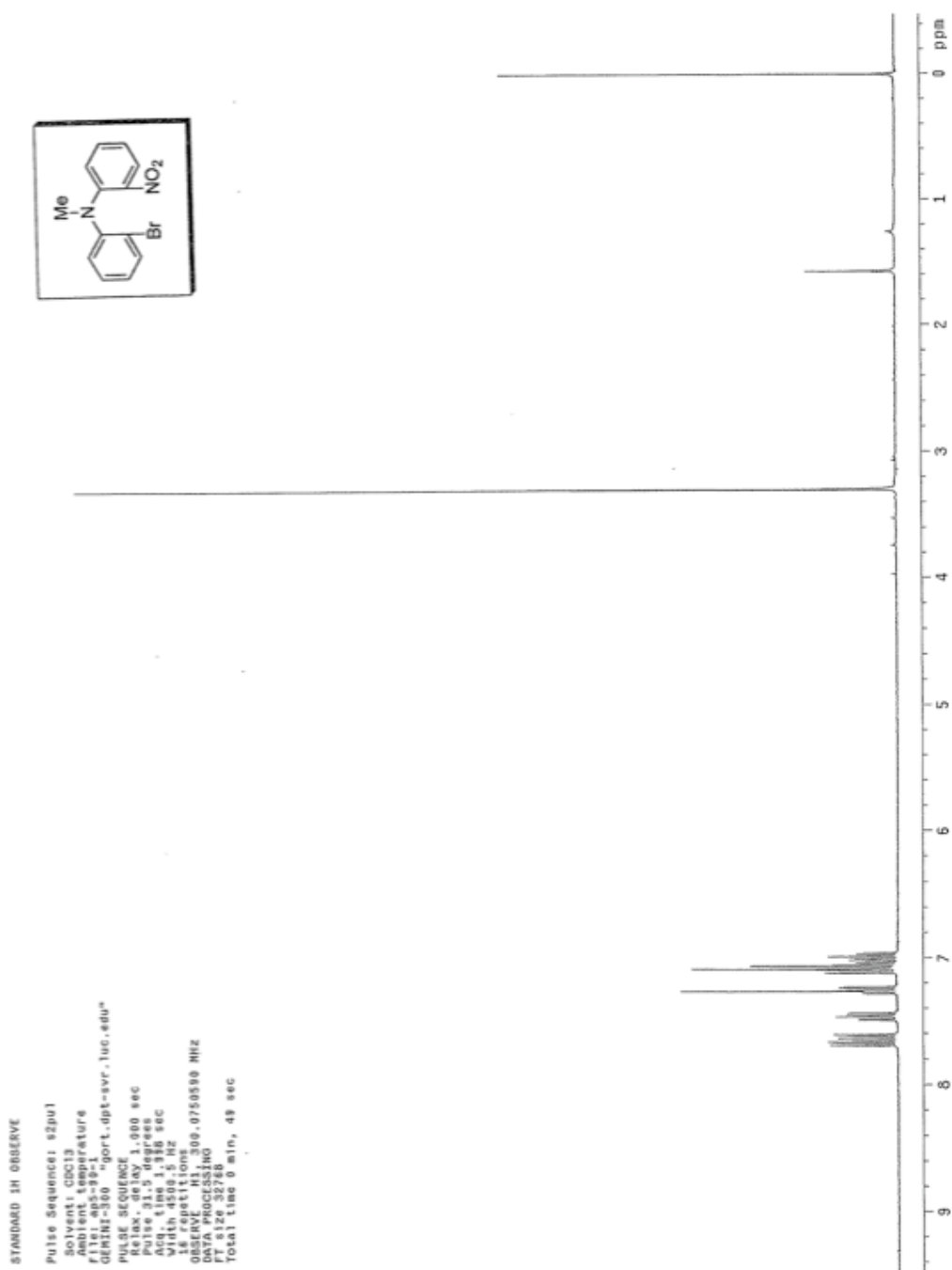
Sample Name	AG1-53-1	Position	PI-A3	Instrument Name	Instrument 1	User Name	Success
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	
Data Filename	AG1-53-1.d	ACQ Method	ESL_ASL_Pos_03122009	Comment		Acquired Time	6/25/2010 10:33:50 AM

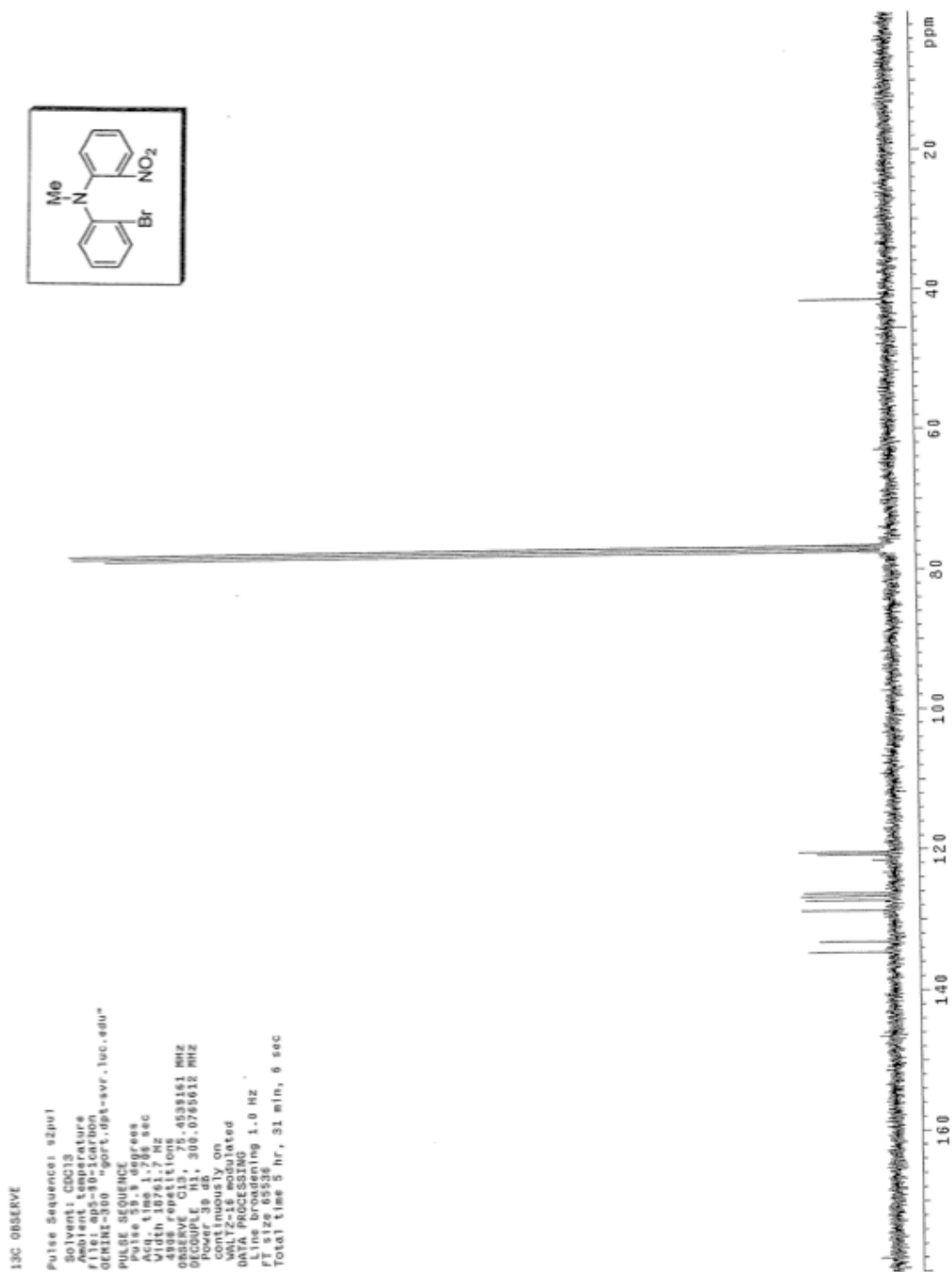


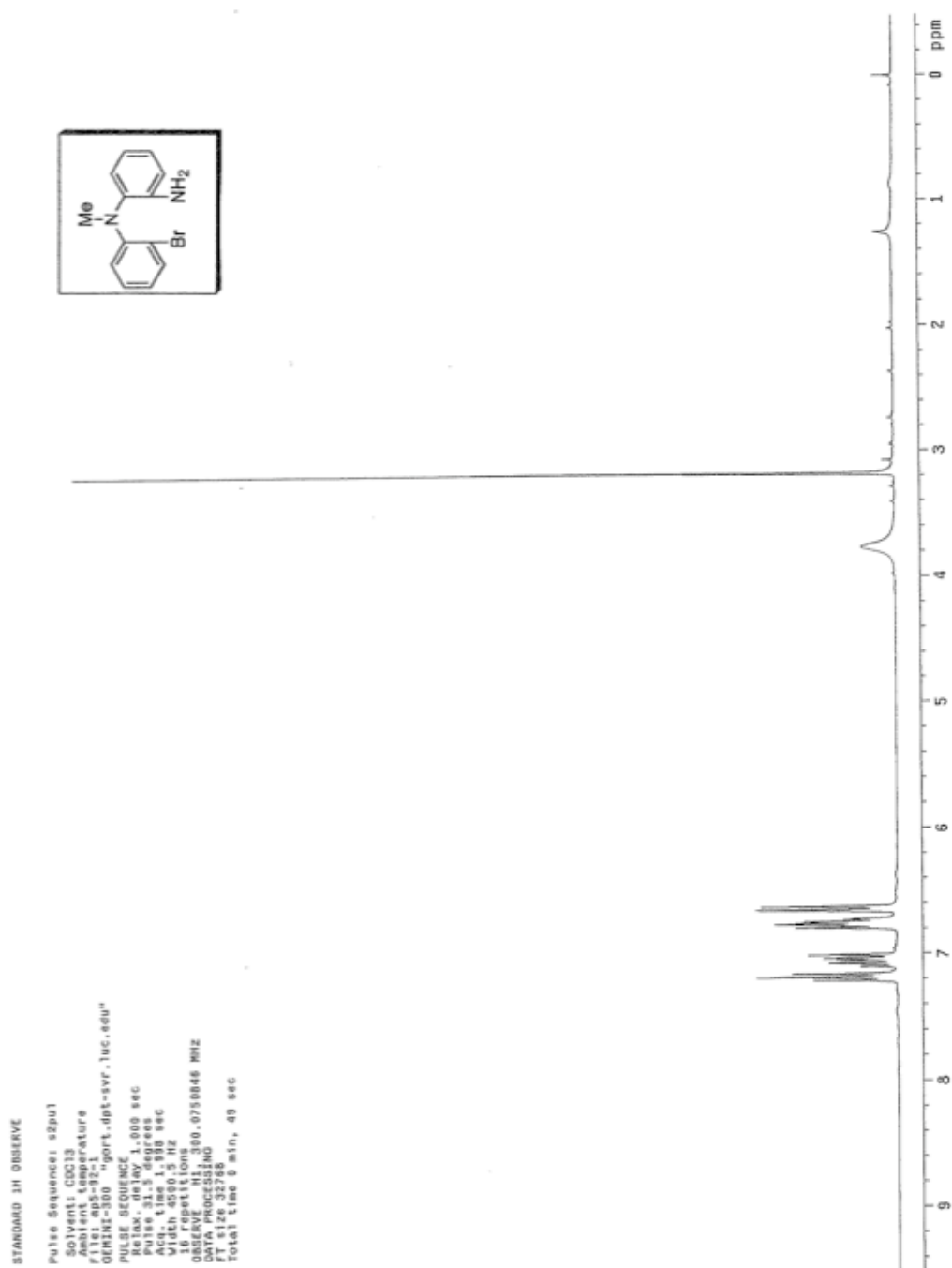
Sample Name AG1-53-1
Inj Vol 2
Data Filename AG1-53-1.d
Position InjPosition
ACQ Method
PI-A3
Instrument Name Sample
SampleType Comment
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:33:50 AM









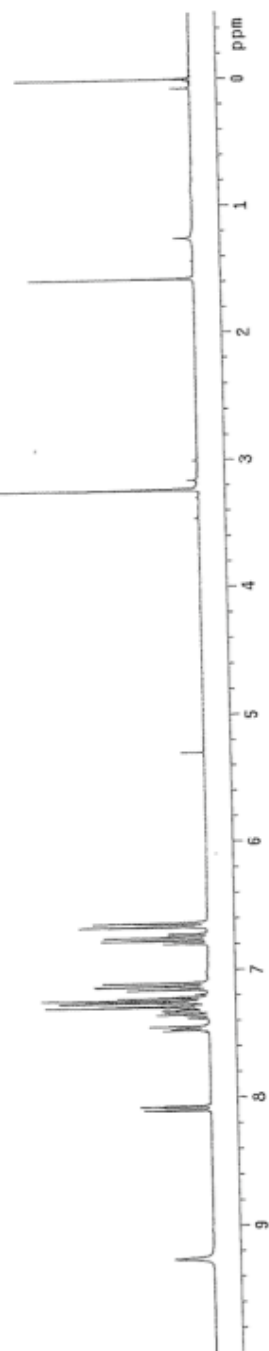
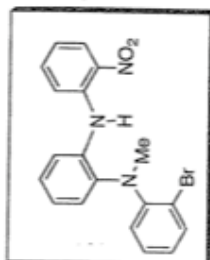






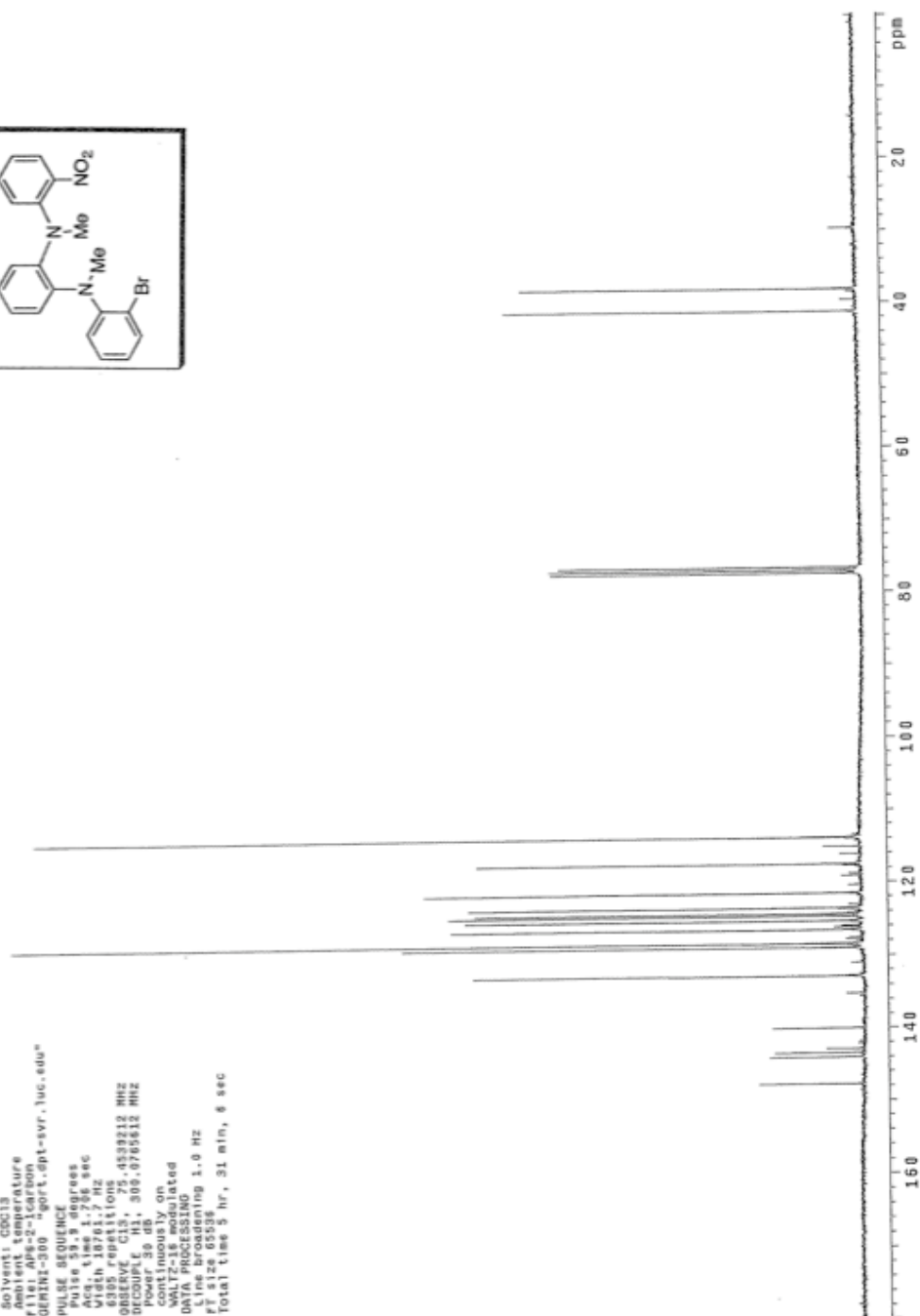
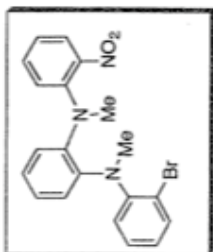
STANDARD IN OBSERVE

Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
File: ap5-95-in
GENI-350 -port.dpt-svr.luc.edu
PULSE SEQUENCE: 1.800 sec
Pulse: 1.800 sec
Pulse: 31.5 degrees
Acq. time 1.350 sec
Width 4550.5 Hz
16 repetitions
Observed frequency 300.0750687 MHz
Observed chemical shift 7.265 ppm
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec

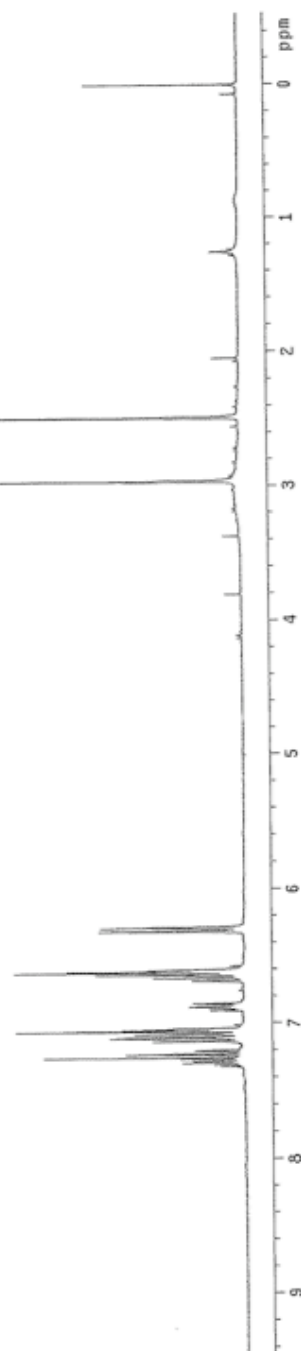
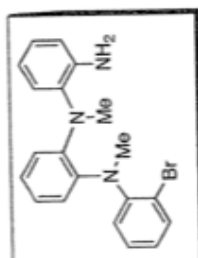


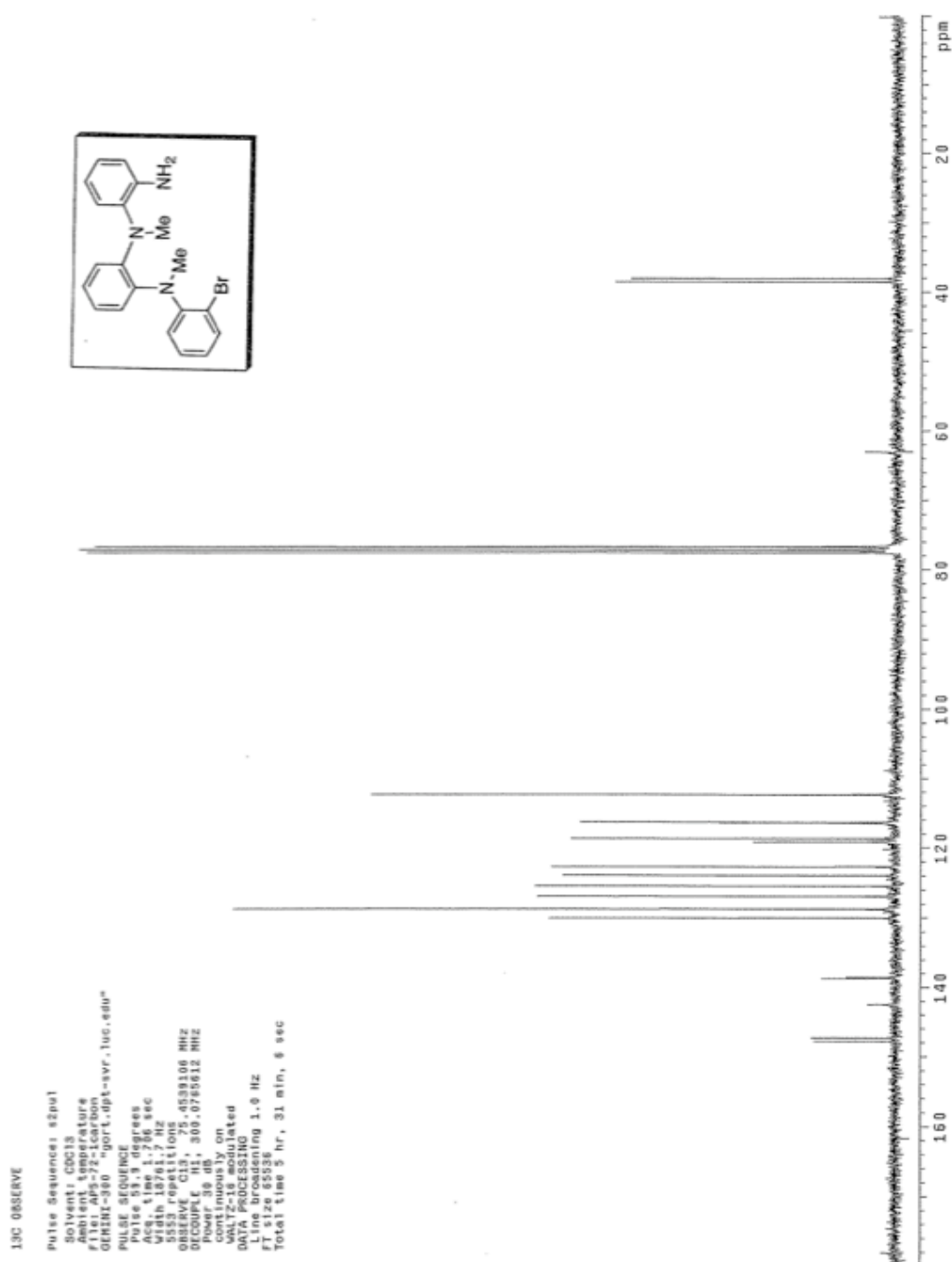
13C OBSERVE

Pulse Sequence: szpul
 Solvent: CDCl3
 Ambient temperature
 1H decoupling: on
 GPMIN-500 "gprt.dpt-svr.luc.edu"
 PULSE SEQUENCE
 Pulse 59.9 degrees
 Acq. time 1.766 sec
 Width 18761.7 Hz
 555V-996110Hz
 OBSERVE: H1, 505.038212 MHz
 DECOUPLE: H1, 505.076513 MHz
 Power 30 dB
 continuously on
 WALTZ-16 decoupled
 DANTE decoupling
 Line broadening 1.0 Hz
 FT size 65536
 Total time 5 hr, 31 min, 6 sec



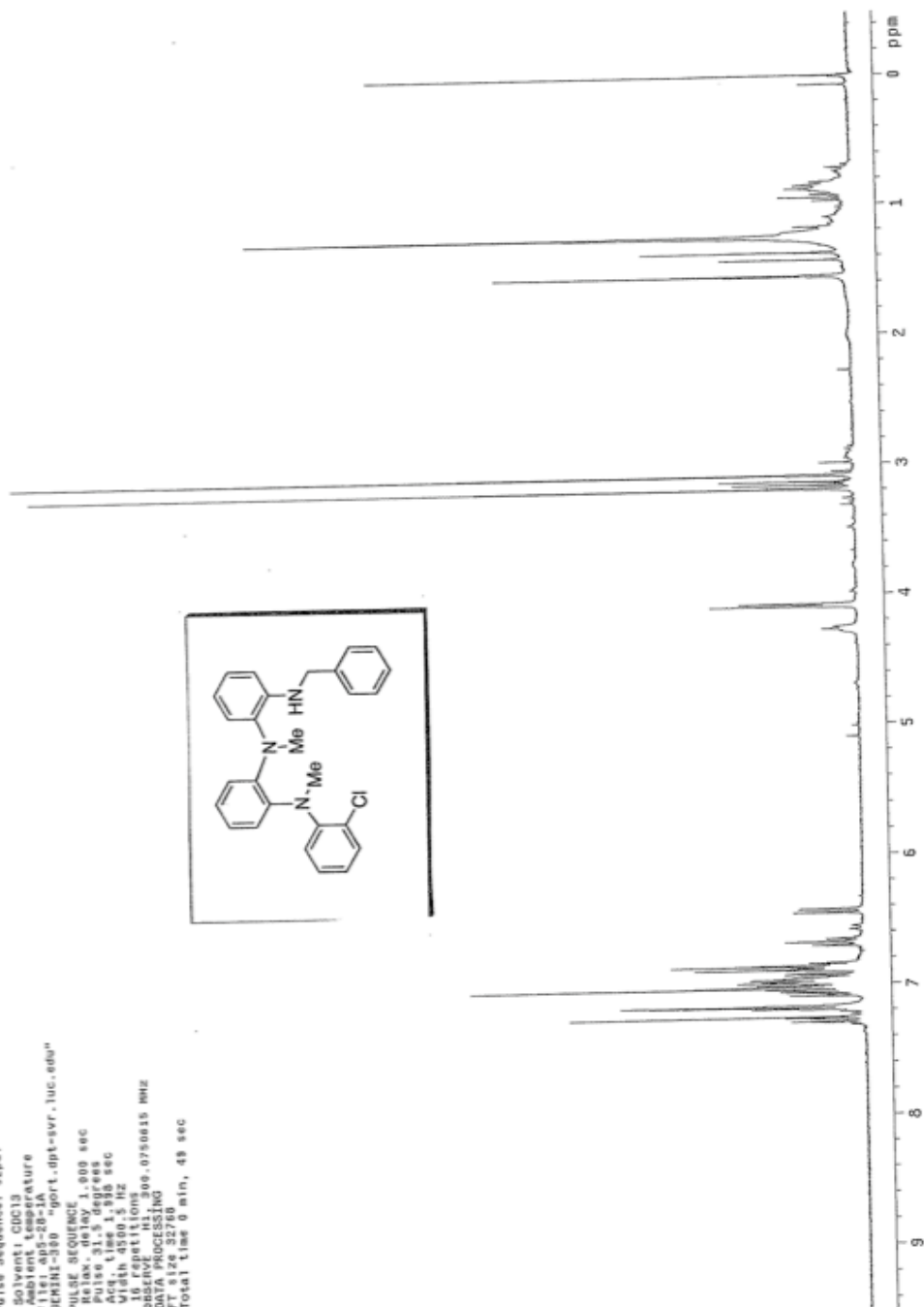
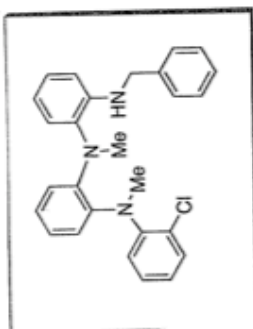
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Acqnt temperature
File: APS-72-1
GENI-300 "gort.dpt-svr.luc.edu"
PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 31.5 degrees
Acqnt time 1.980 sec
Width 060.5 Hz
16 repetitions
OBSERVE H1,300.0750082 MHz
DATA PROCESSING
F1 H1,300.0750082 MHz
Total time 0 min, 43 sec





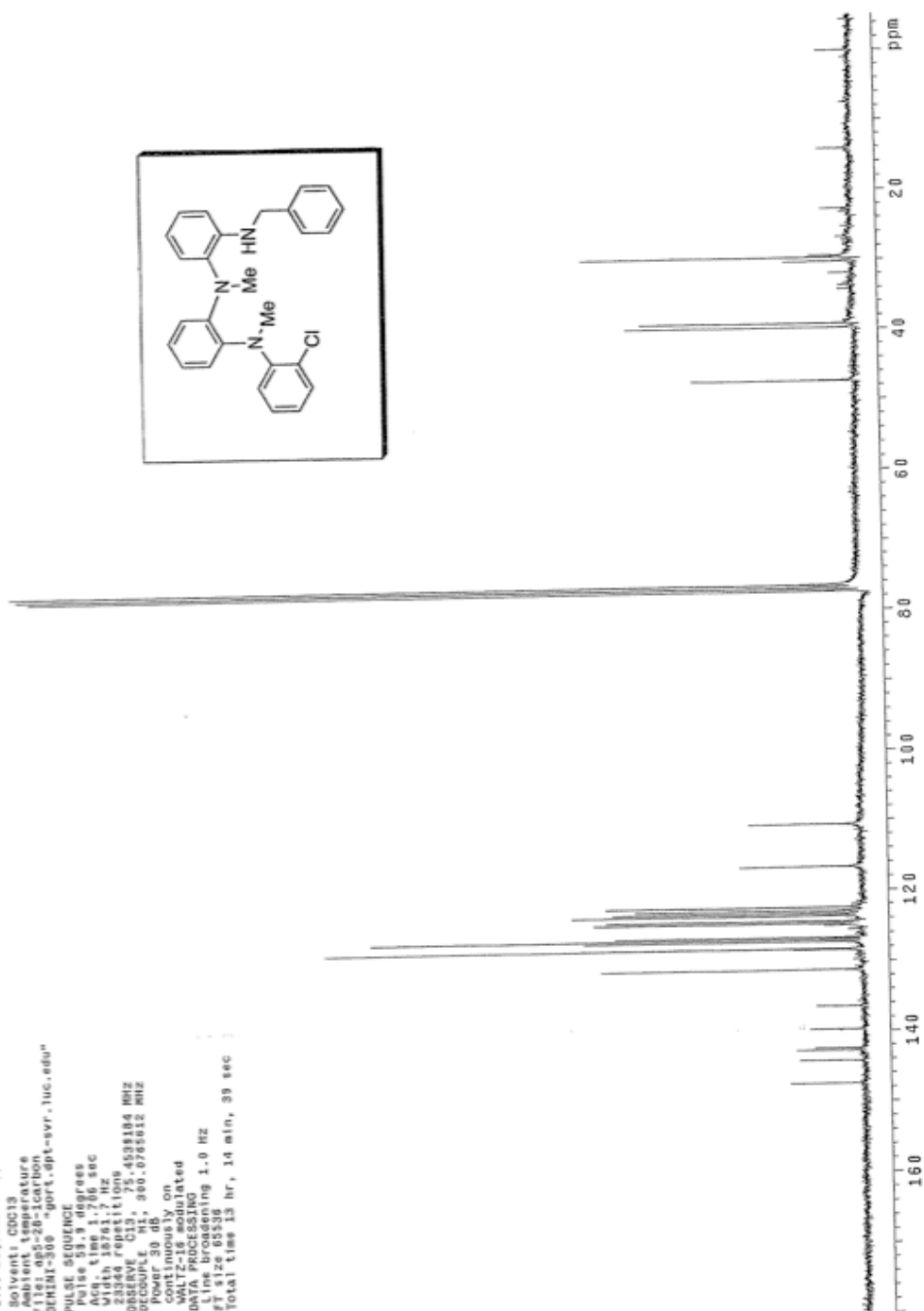
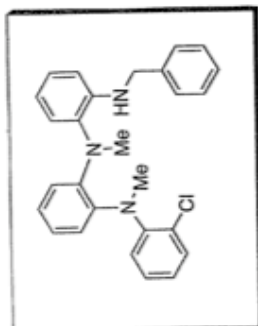
STANDARD IN OBSERVE

Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: ap5-29-1A
GCHN1-350 -port.dpt-svr.luc.edu
PULSE SEQUENCE: zgpg30
Pulse program: zgpg30
Pulse, 31.5 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
Observed frequency 0750615 MHz
SOLVENT: CDCl3
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec

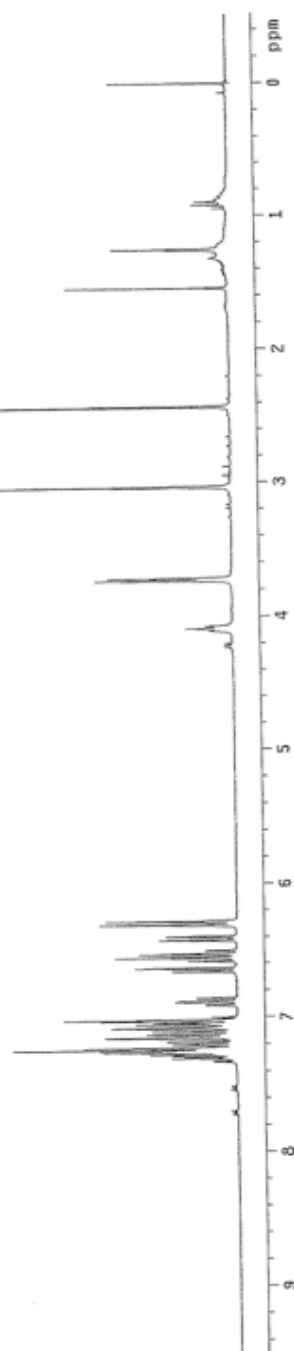
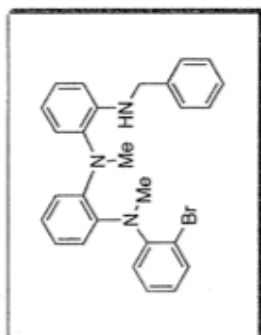


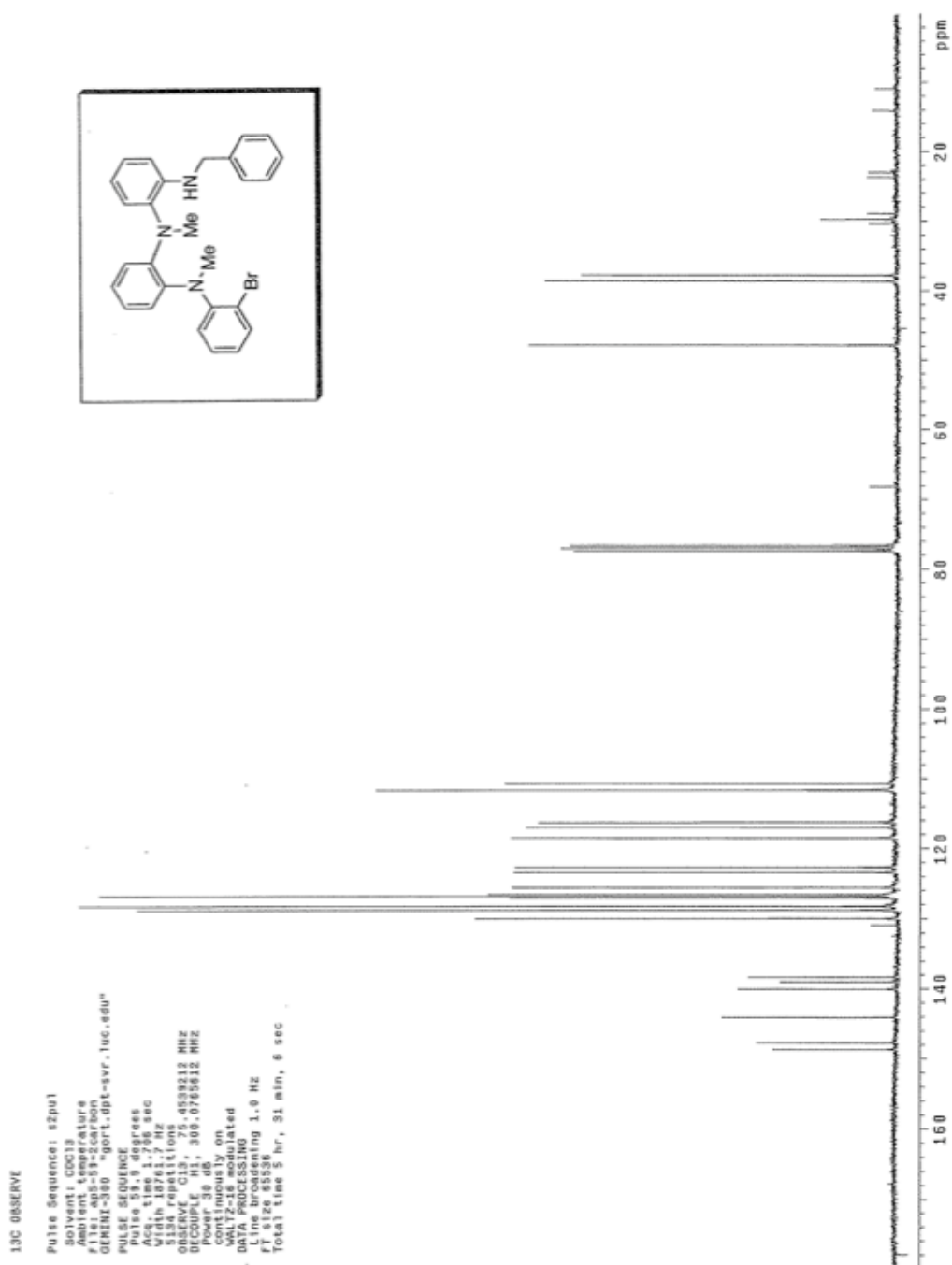
13C OBSERVE

Pulse Sequence: szpu1
 Solvent: CDCl3
 Ambient Temperature
 File: dg5-28-1carbon
 GEMINI-300 -port.dft-svr.luc.edu
 PULSE SEQUENCE
 13C zgpg30
 Delay 1.000000 sec
 Width 18761.7 Hz
 23344 repetitions
 OBSERVE C13, 75.453184 MHz
 OBSERVE C13, 999.975512 MHz
 Power 30 dB
 Modulated continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Time Resolving 1.0 Hz
 File 28 85538
 Total time 13 hr, 14 min, 39 sec



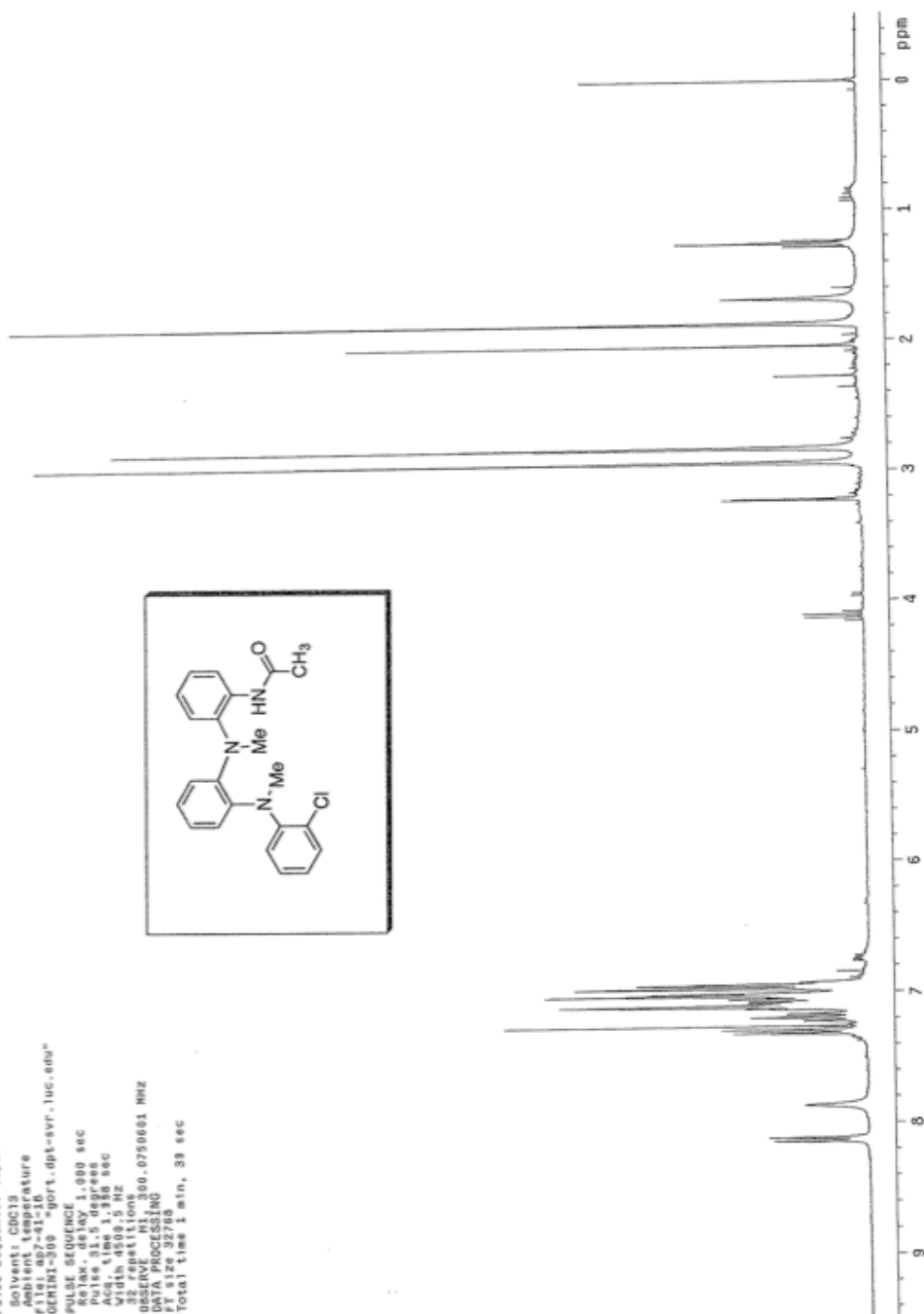
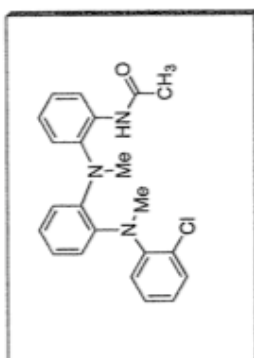
STANDARD IN OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl₃
P1: 1.50 sec
Temperature
File: MS-58-2
GEMINI-300 "gort.dpt-svr.luc.edu"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. 1.000 sec
With 450.5 MHz
16 repetitions
OBSERVE N1: 306.0750664 MHz
DATA PROCESSING
F1 size 32768
Total time 0 min, 48 sec

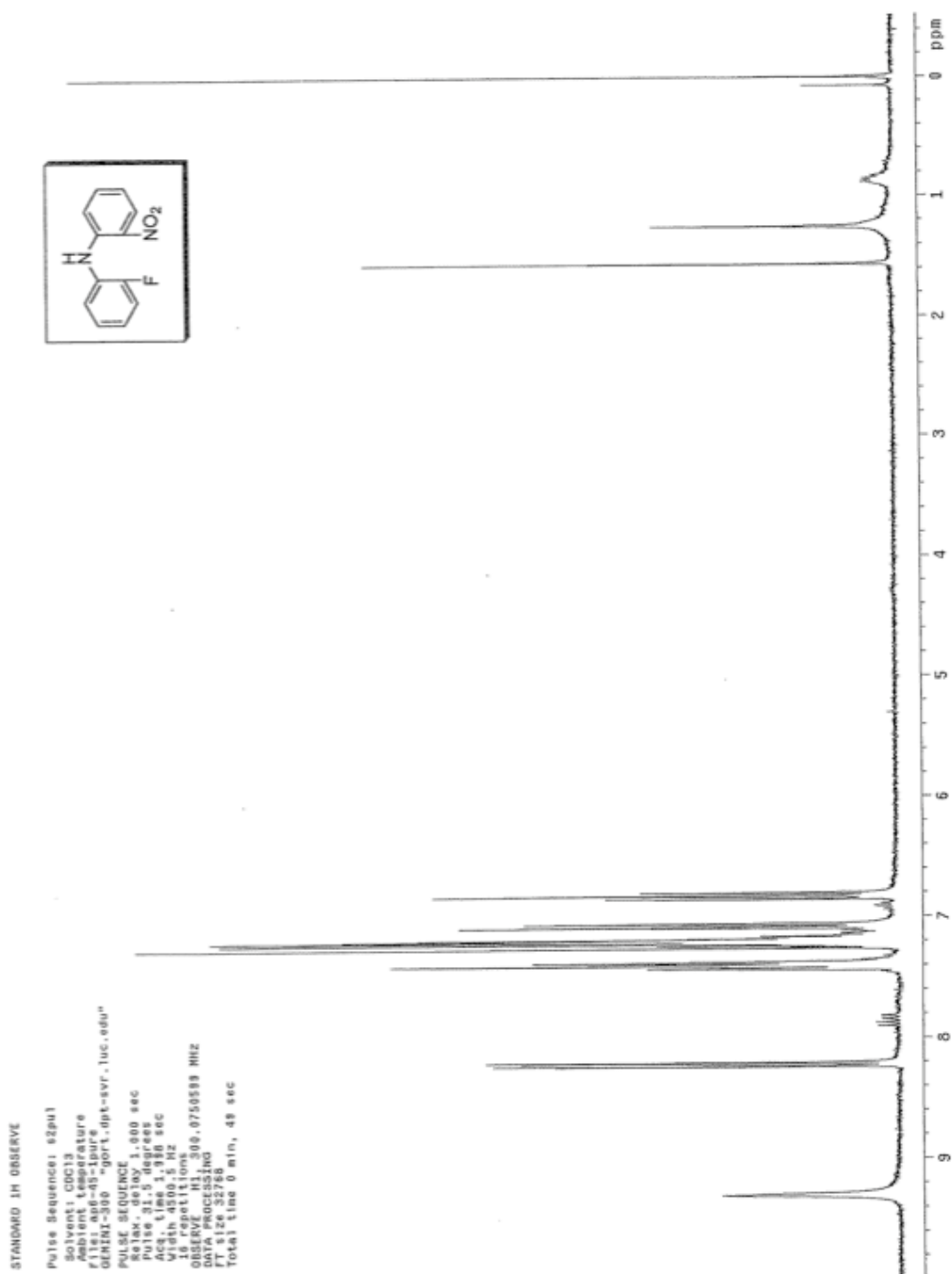


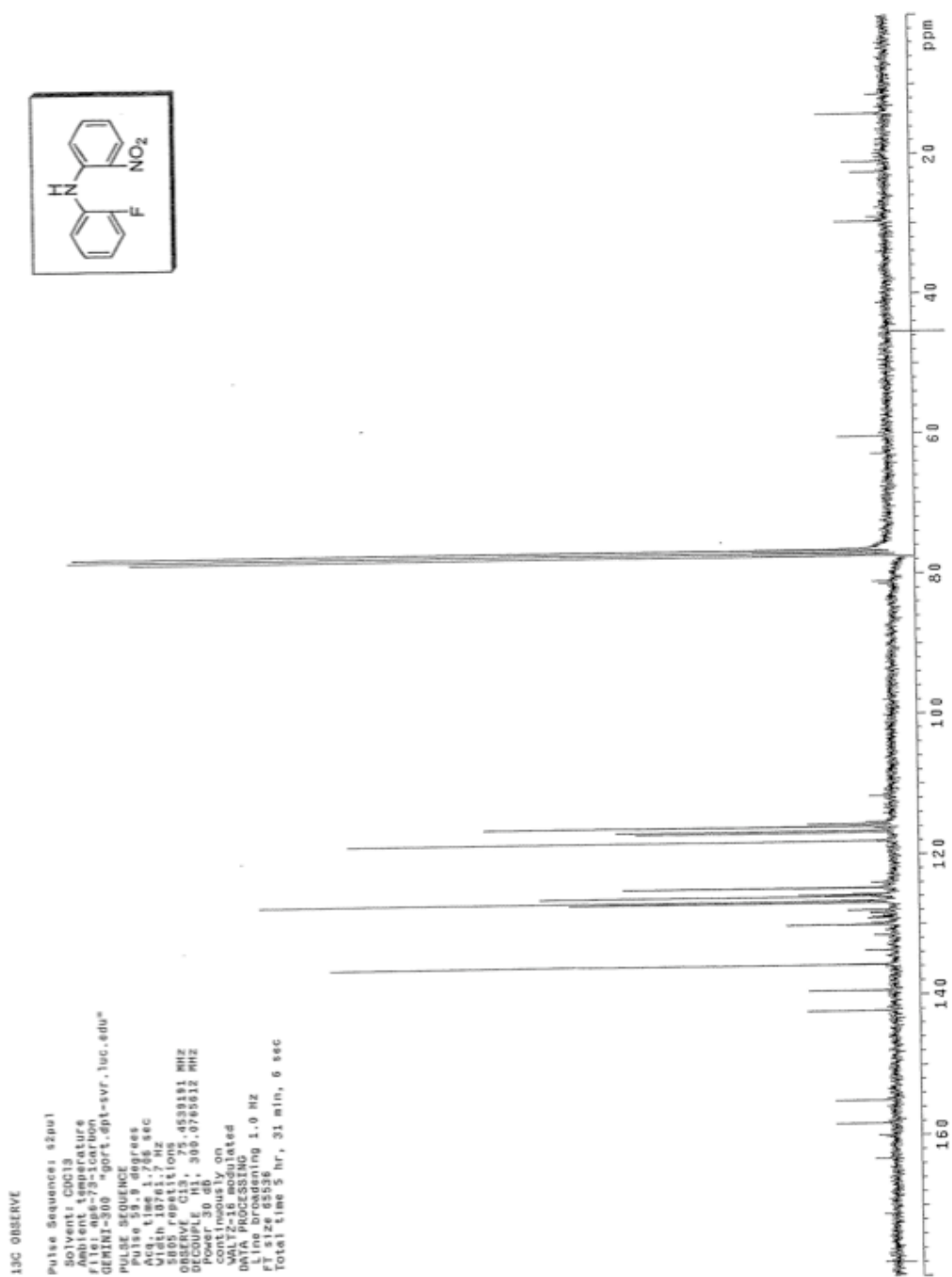
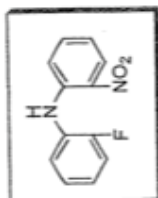


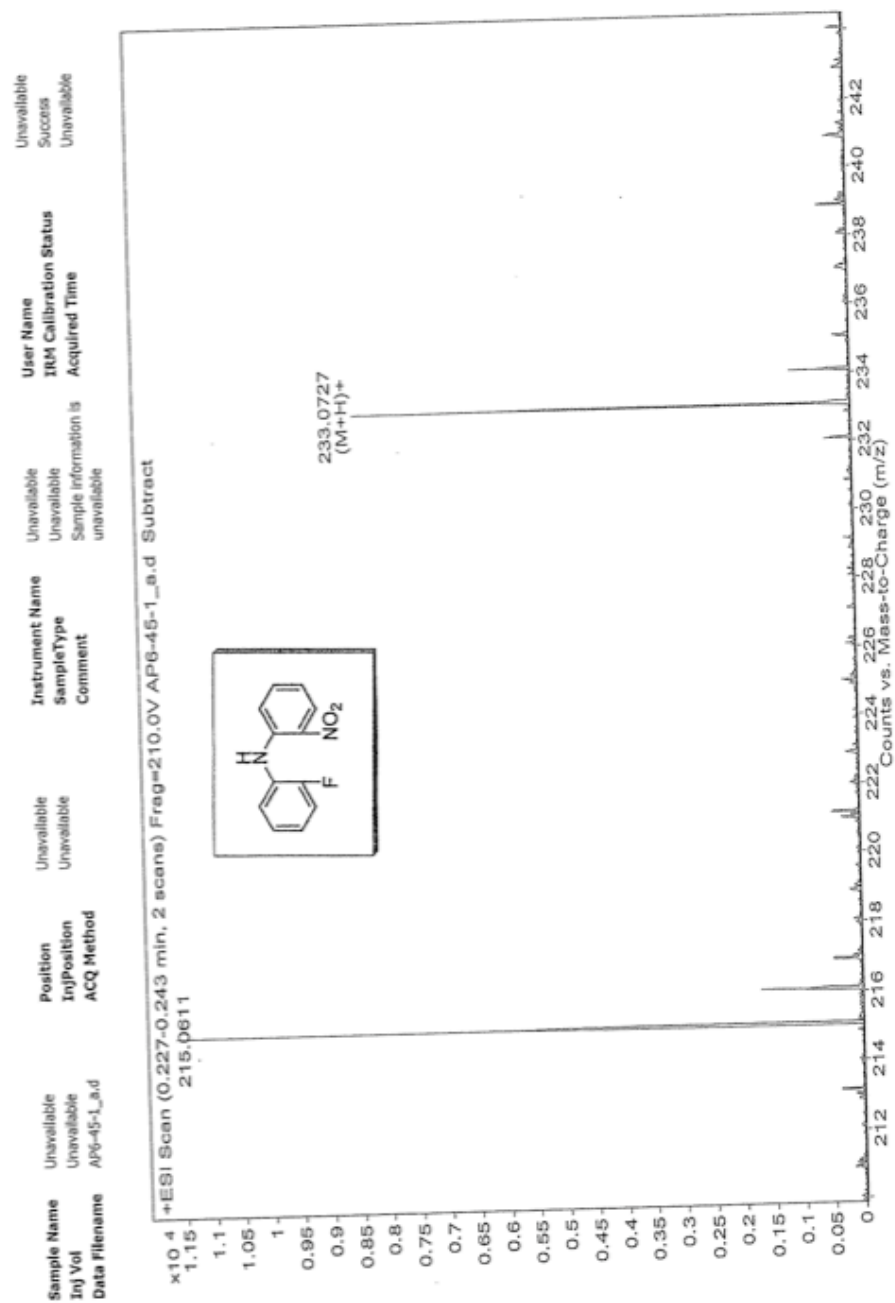
STANDARD 1H OBSERVE

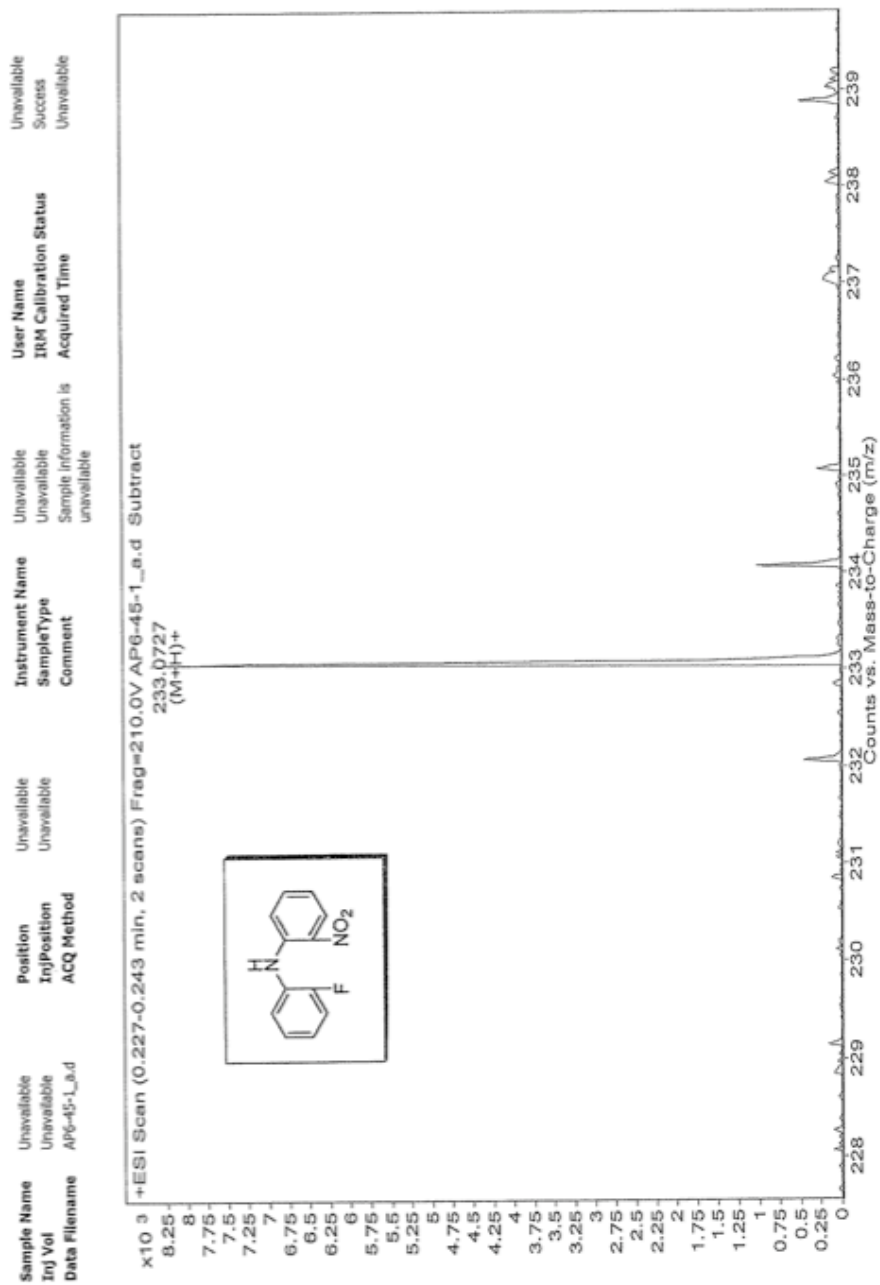
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
F1 (ppm) 100.625
GENI-300 -port.dpt-svf.luc.edu
PULSE SEQUENCE
Relax delay 1.000 sec
Pulse 31.5 degrees
Acq. time 1.388 sec
Width 4000 Hz
F2 (ppm) 100.625
OBSERVE F1 300.0750691 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 38 sec

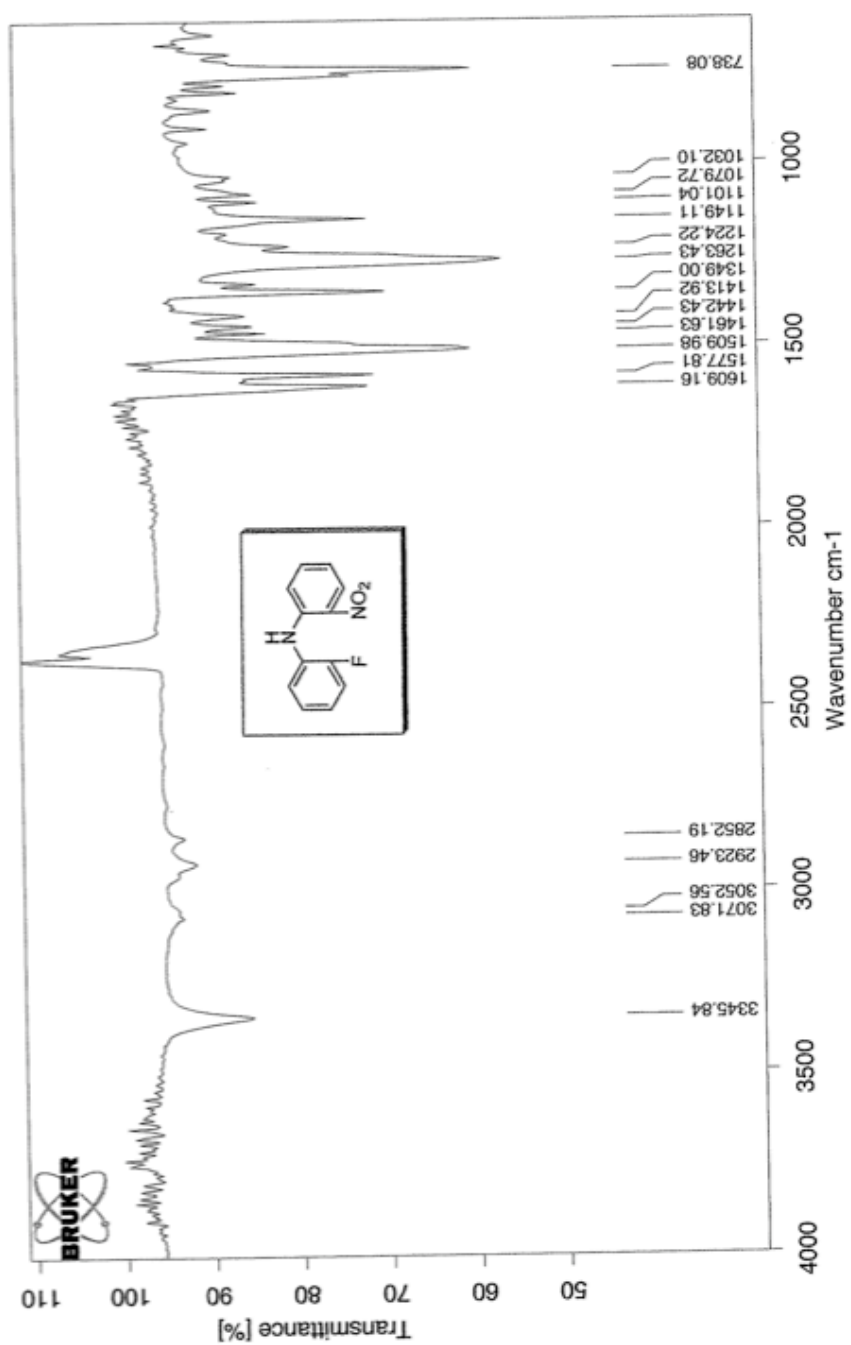










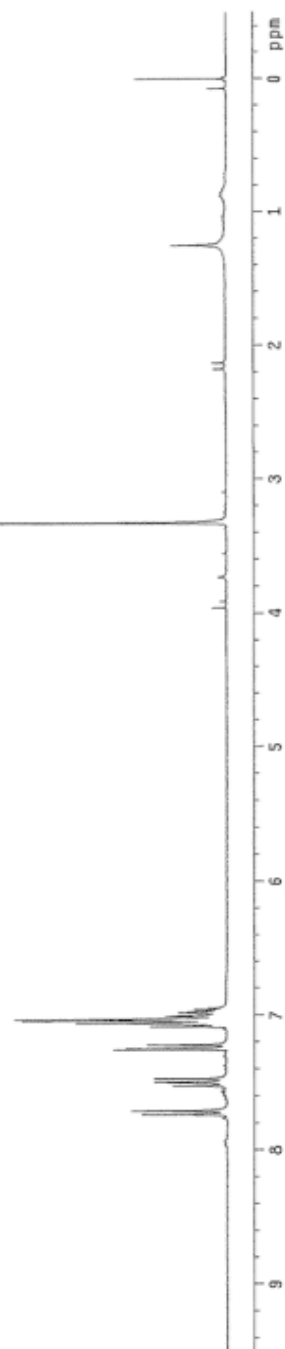
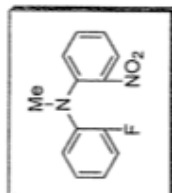


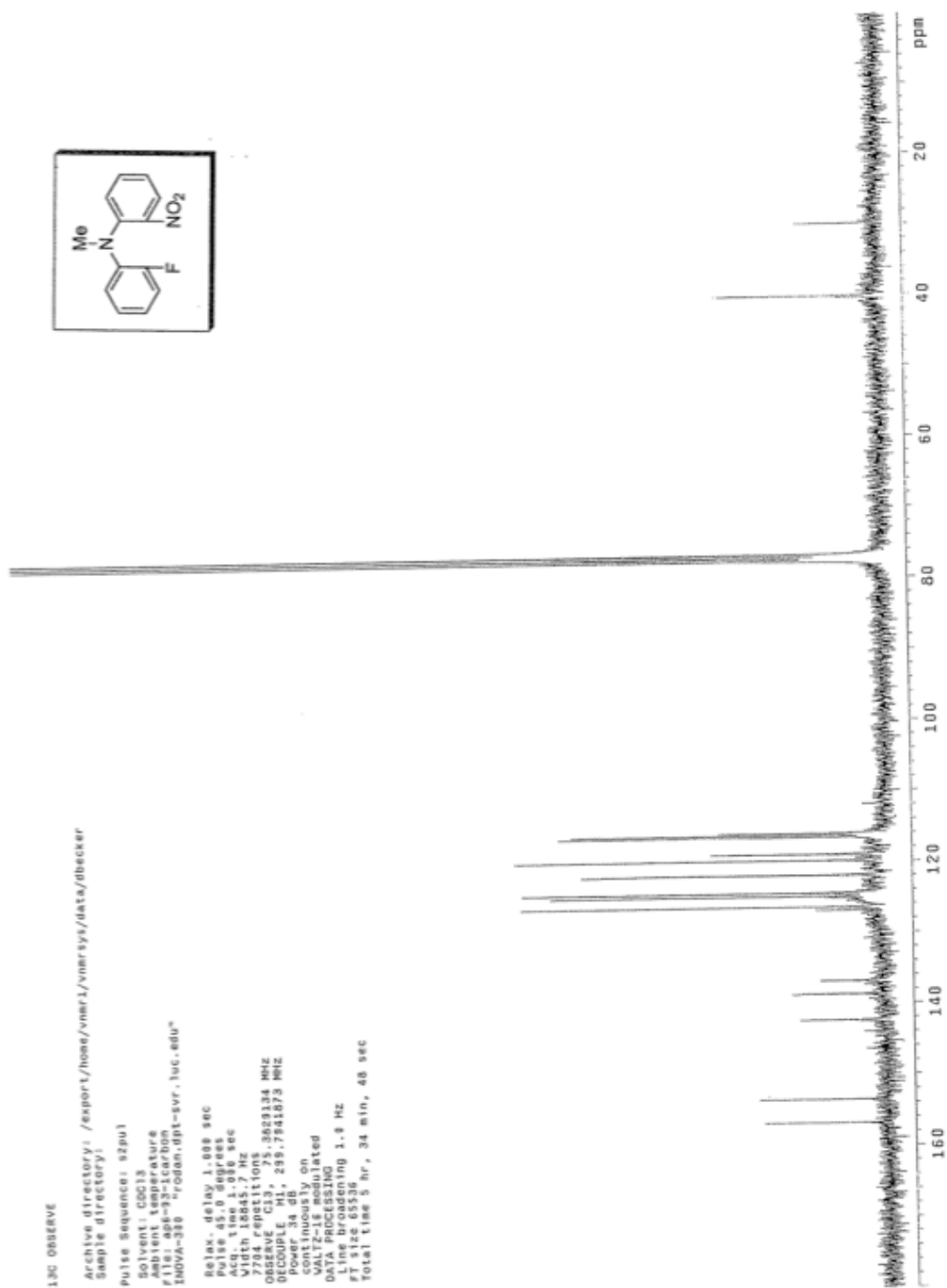
07/06/2010

Instrument type and / or accessory

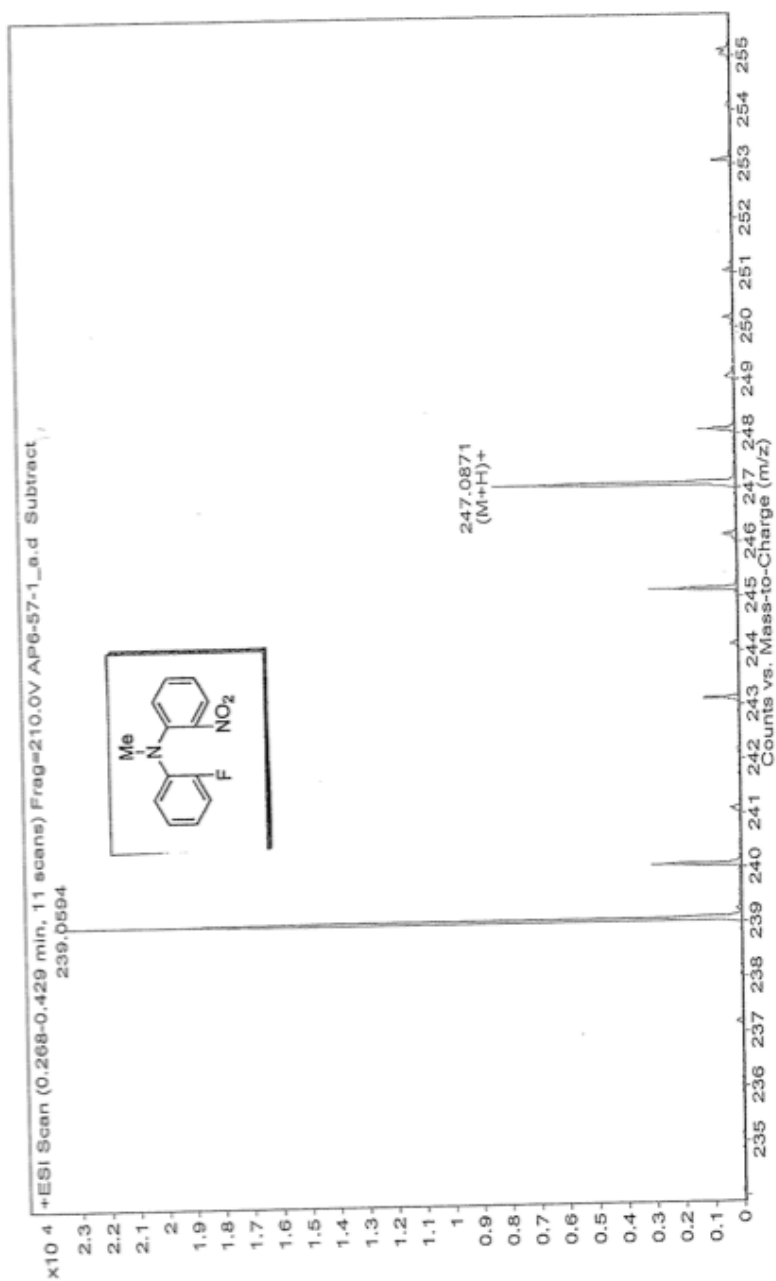
C:\Program Files\OPUS_65\Data\AP6 B.1

STANDARD 1H OBSERVE
Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
File: sps-57-1
GEMINI-300 -gort.dpt-svr.luc.edu
PULSE SEQUENCE
Relax delay 1.000 sec
Pulse delay 0.000 sec
Acq time 1.918 sec
Width 4500.5 Hz
16 repetitions
OBSERVE: H1 300.0750604 MHz
GEMINI-300
FT size 32768
Total time 9 min, 49 sec

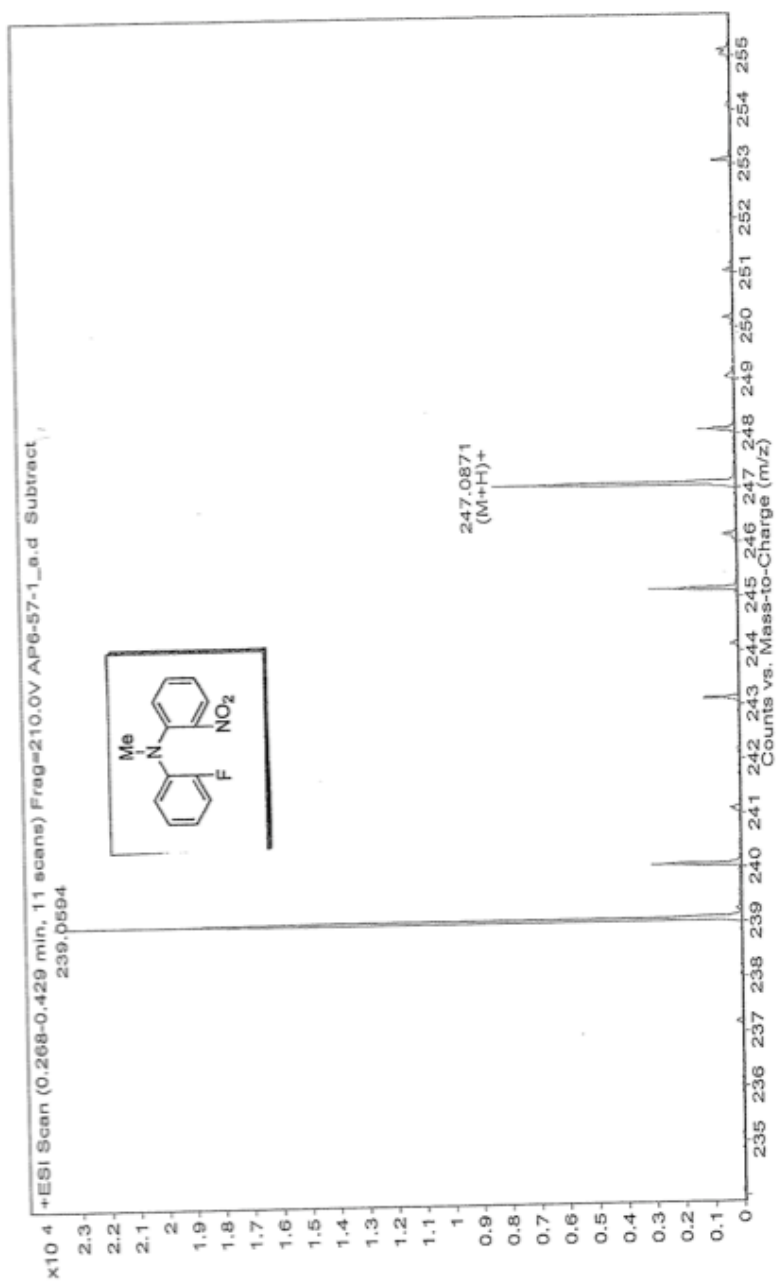




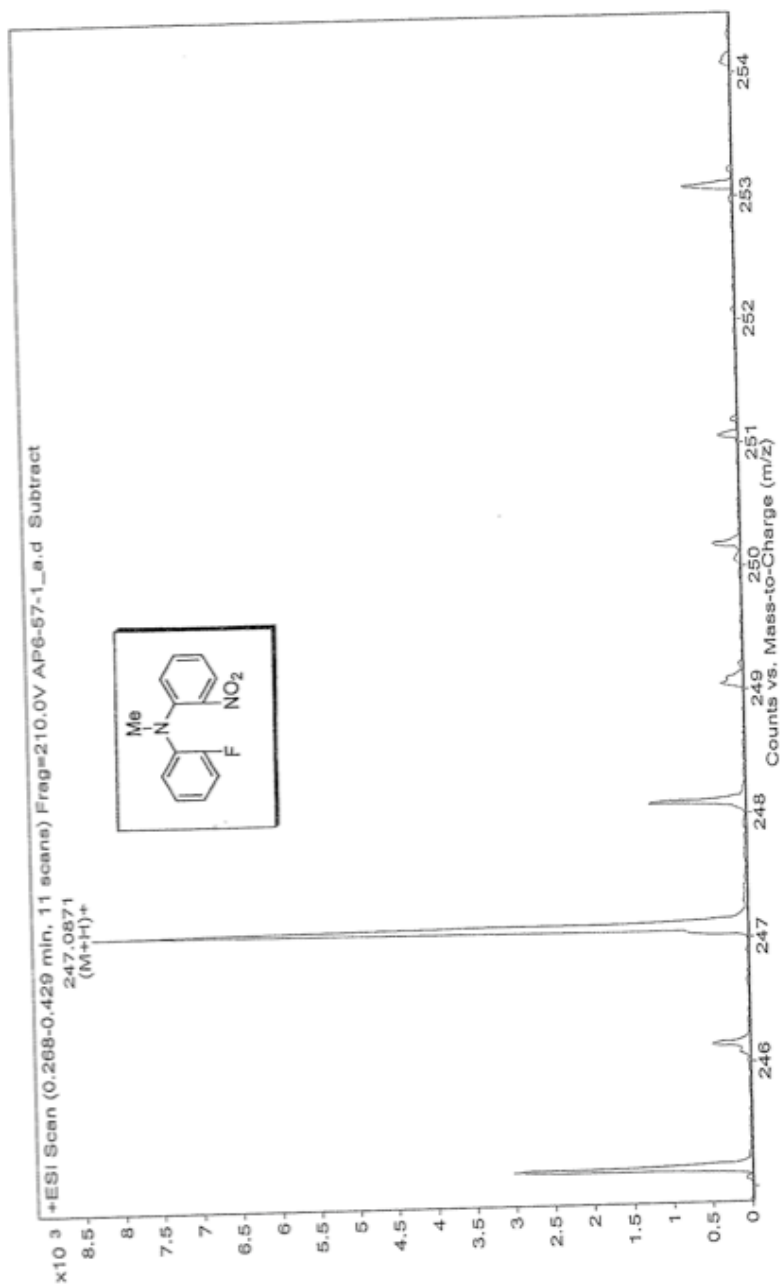
Sample Name AP6-S7-1
Inj Vol 5
Data Filename AP6-S7-1_a.d
Position InjPosition
ACQ Method
P1-AS
Instrument Name Sample
SampleType Comment
ESL_ASL_Pos_03122009
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 11:34:54 AM

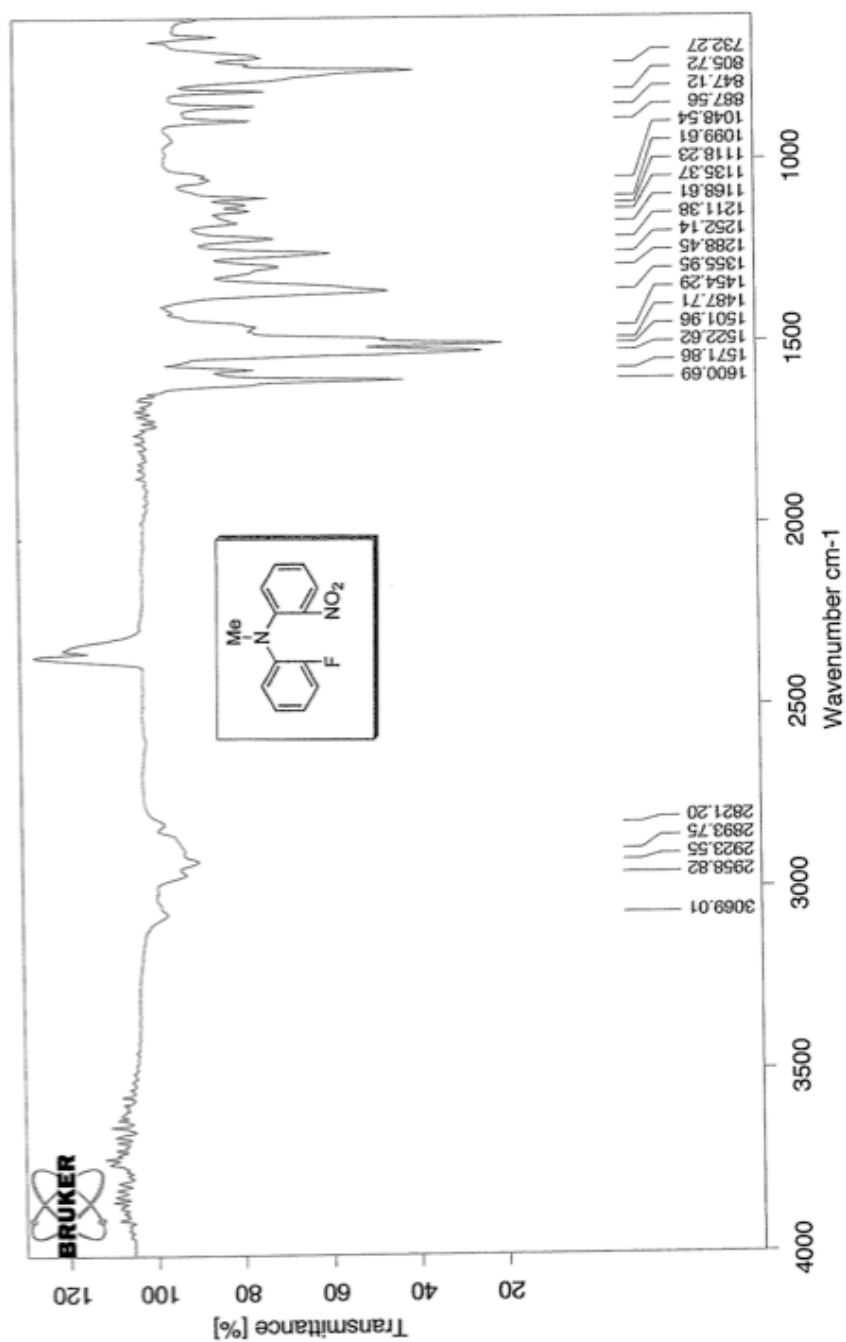


Sample Name AP6-S7-1
Inj Vol 5
Data Filename AP6-S7-1_a.d
Position InjPosition
ACQ Method
P1-AS
Instrument Name Sample
SampleType Comment
ESL_ASU_Pos_03122009
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 11:34:54 AM



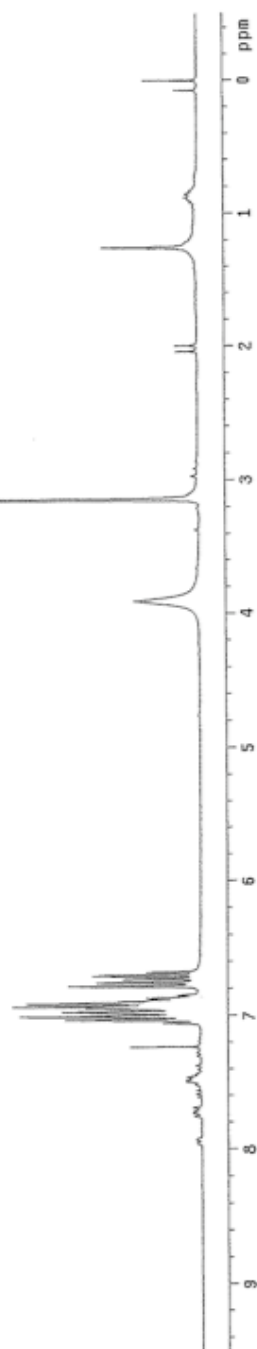
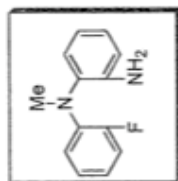
Sample Name	AP6-57-1	Position	P1-A5	Instrument Name	Instrument 1	User Name	Success
Inj Vol	5	InjPosition	ESI_ASL_Pos_03122009	SampleType	Sample	IRM Calibration Status	6/25/2010 11:34:54 AM
Data Filename	AP6-57-1.d	ACQ Method		Comment		Acquired Time	

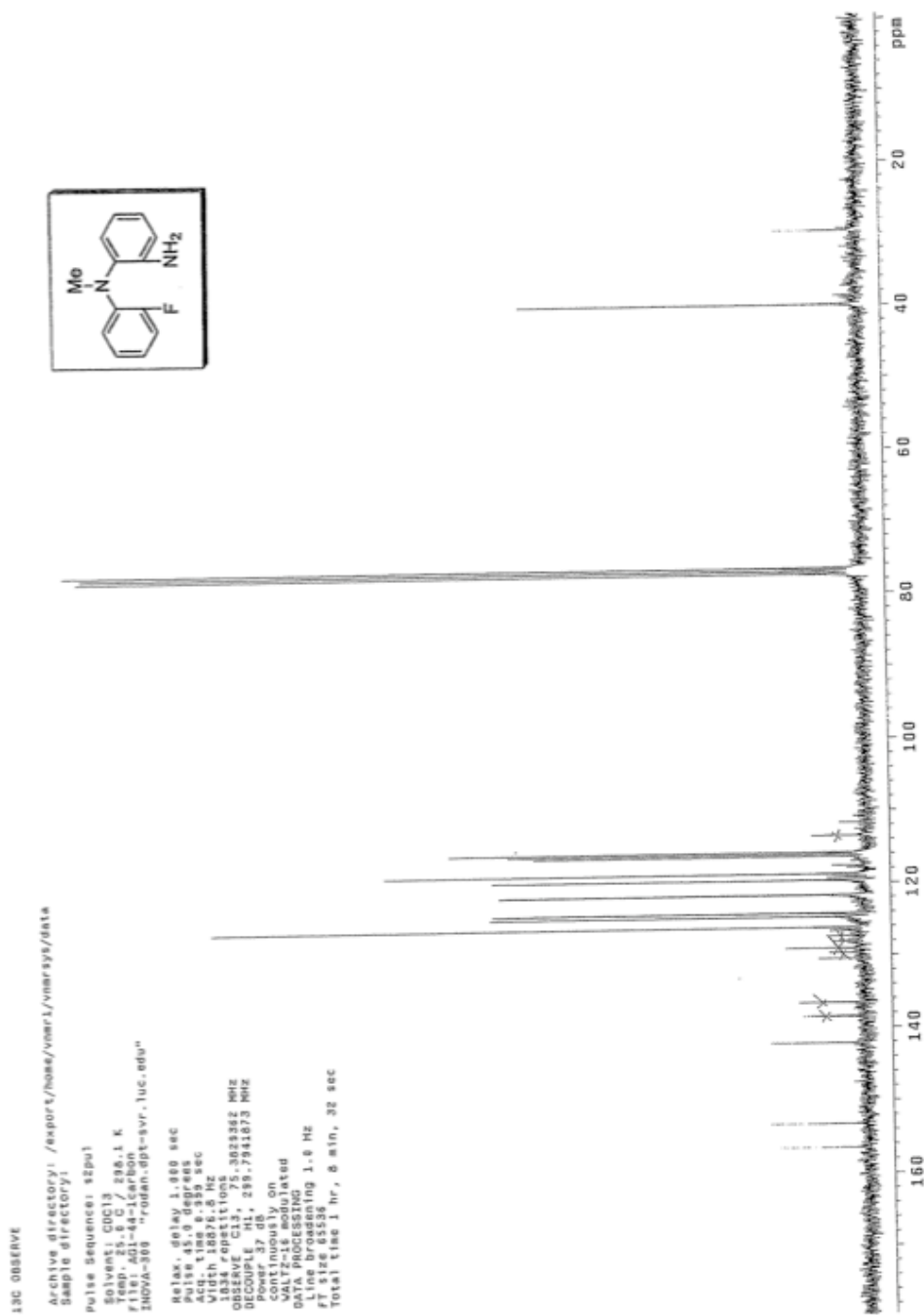


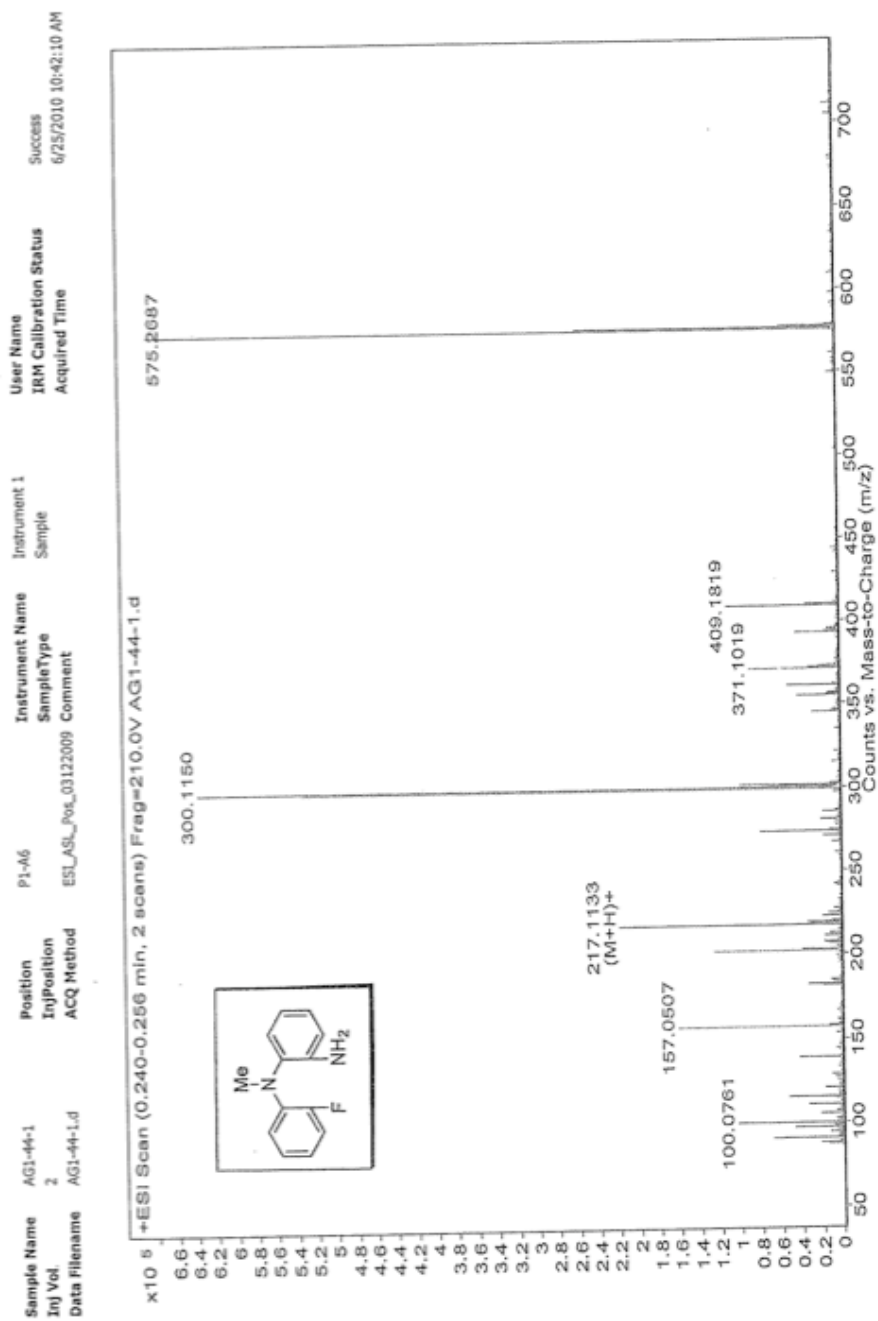


C:\Program Files\OPUS_65\Data\AP6 B.2	Instrument type and / or accessory	07/06/2010
---------------------------------------	------------------------------------	------------

STANDARD 1H OBSERVE
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
F1H1: 400-MS-1
GENIUS-300 -gort.dpt-svr.luc.edu
PULSE SEQUENCE 1.500 sec
Pulse 1.500 sec
Pulse 31.5 degrees
Acq. time 1.500 sec
Width 4500.5 Hz
10 repetitions
Observed frequency 0.0750081 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec







Sample Name AG1-44-1
Inj Vol 2
Data Filename AG1-44-1.d

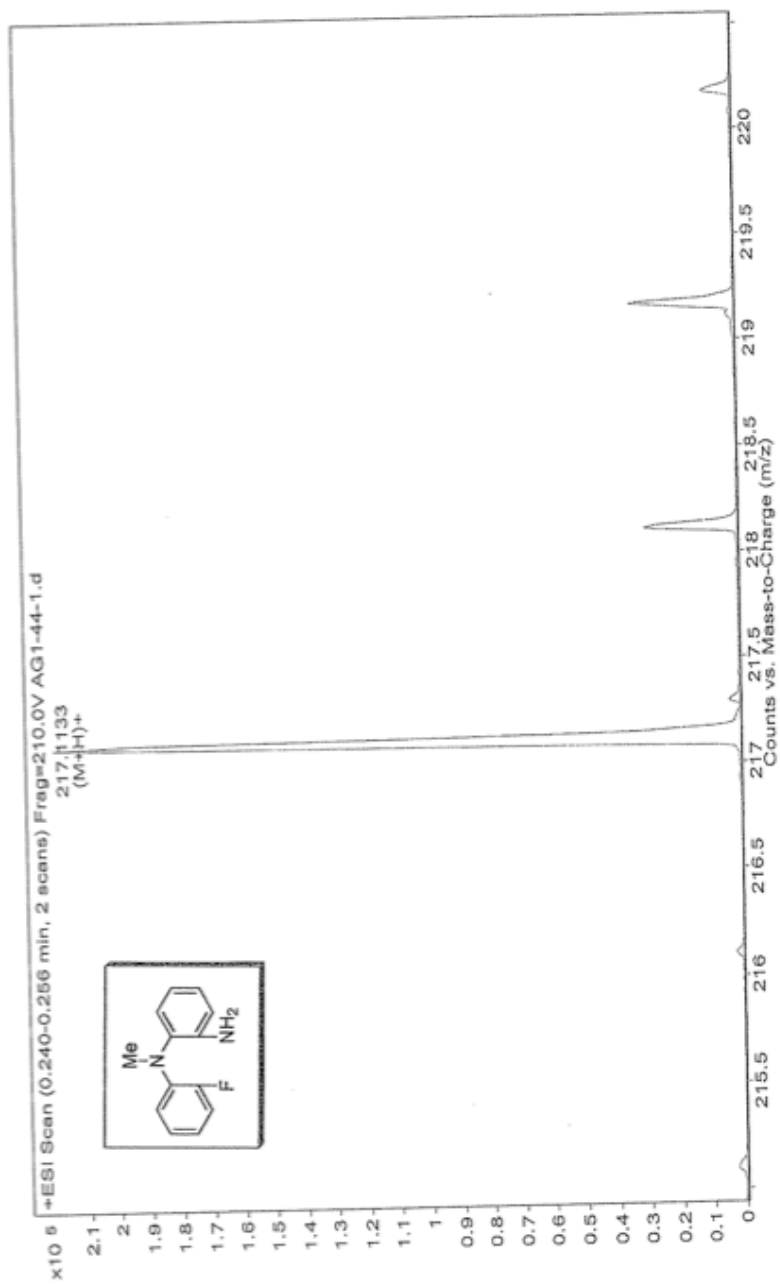
Position
InjPosition
ACQ Method

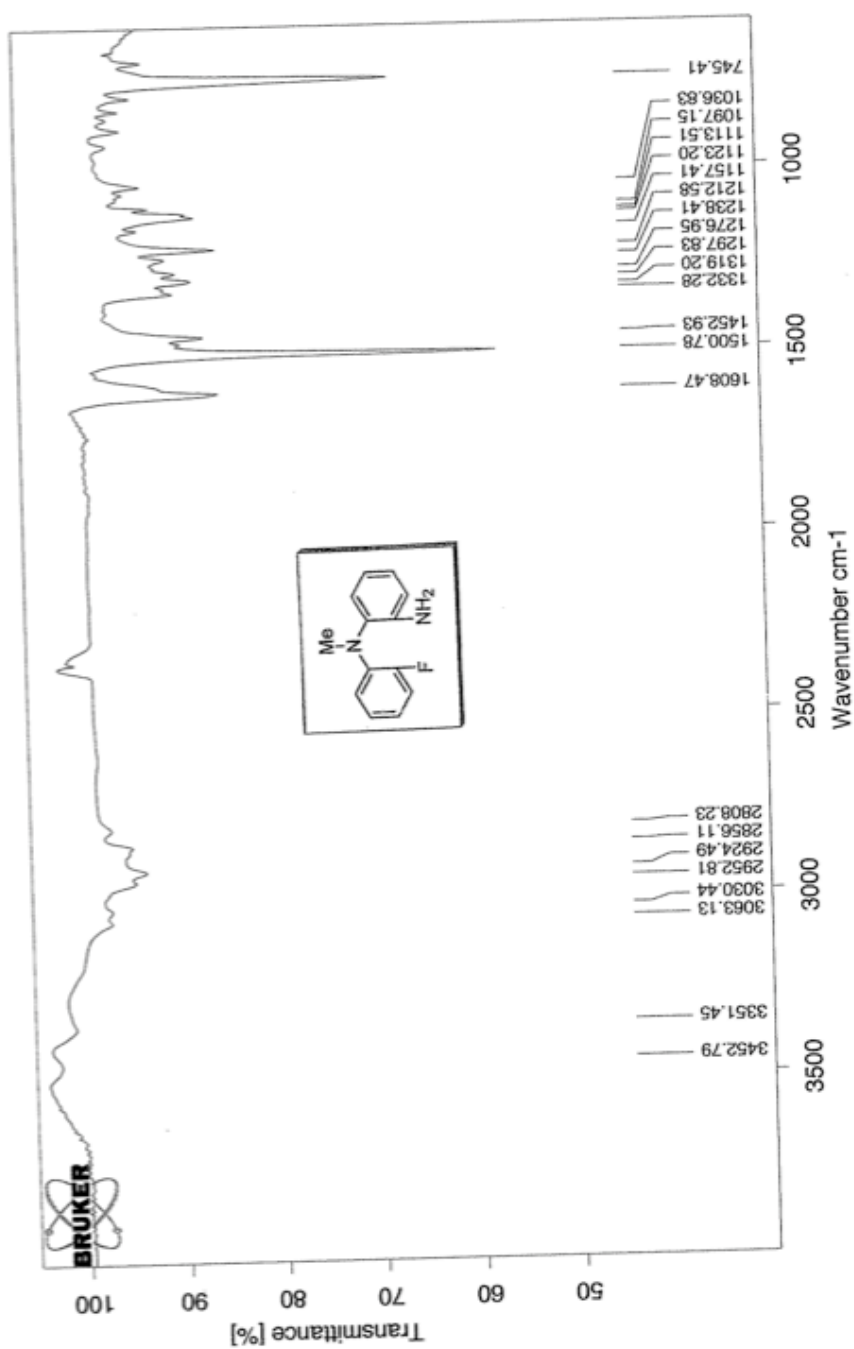
Instrument Name
SampleType
Comment

Instrument 1
Sample

User Name
IRM Calibration Status
Acquired Time

Success
6/25/2010 10:42:10 AM





07/06/2010

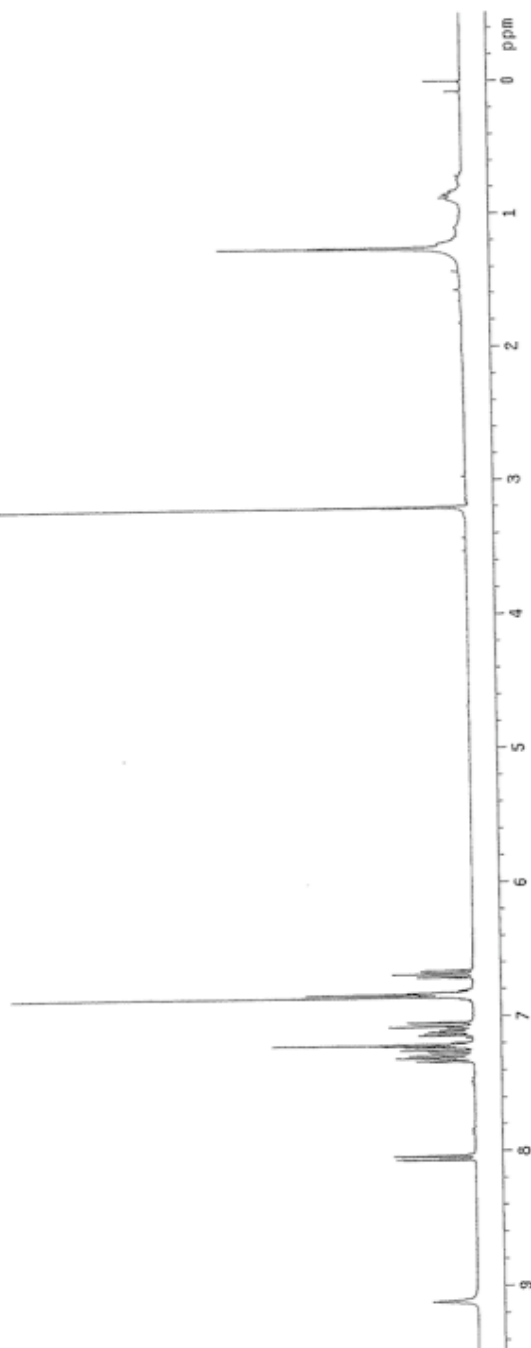
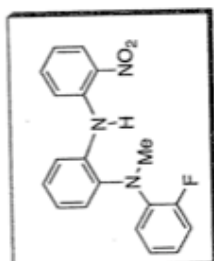
Instrument type and / or accessory

C:\Program Files\OPUS_65\Data\AP6 B.4

Page 1/1

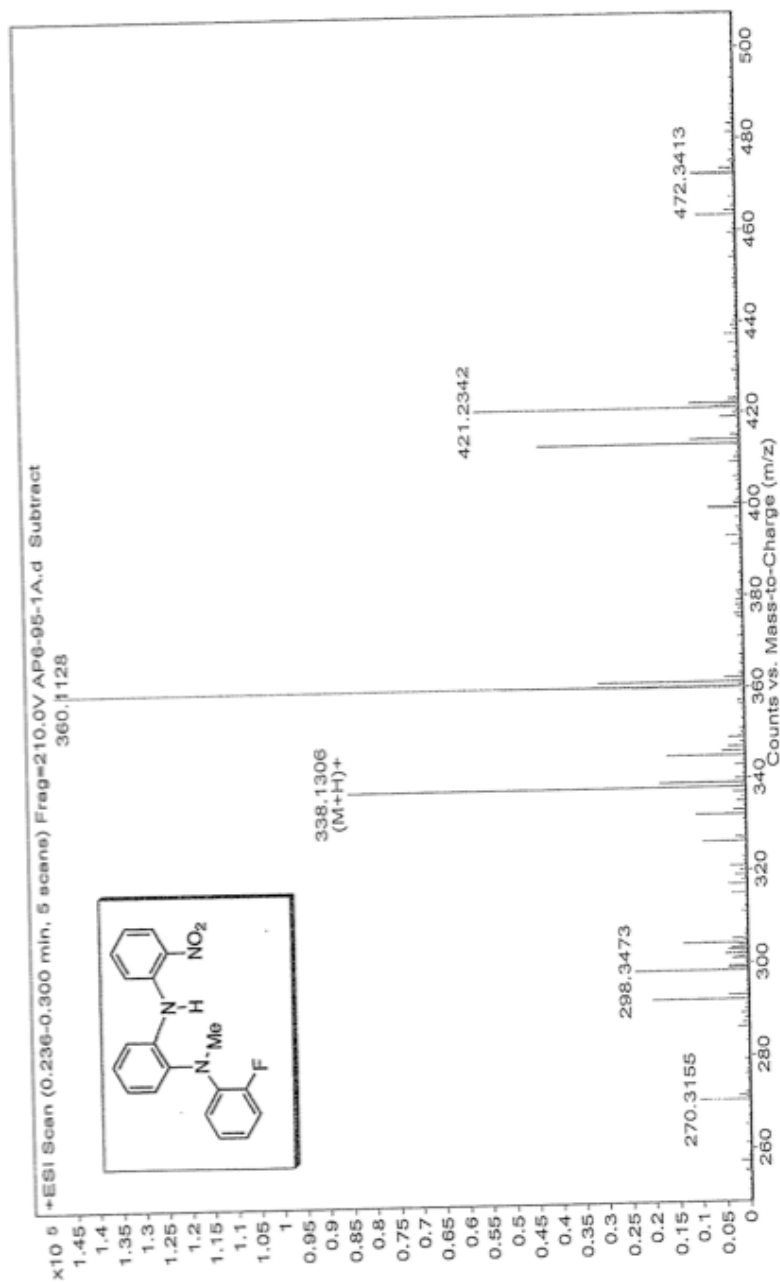
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Acquisition Temperature
 F1: 400-101498
 GENI: 300 -gort.dpt-svf.luc.edu
 PULSE SEQUENCE
 Relax delay 1.000 sec
 Pulse 31.0 degrees
 Acq. time 1.300 sec
 16 repetitions
 OBSERVE: M1, 300.0750025 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min, 49 sec

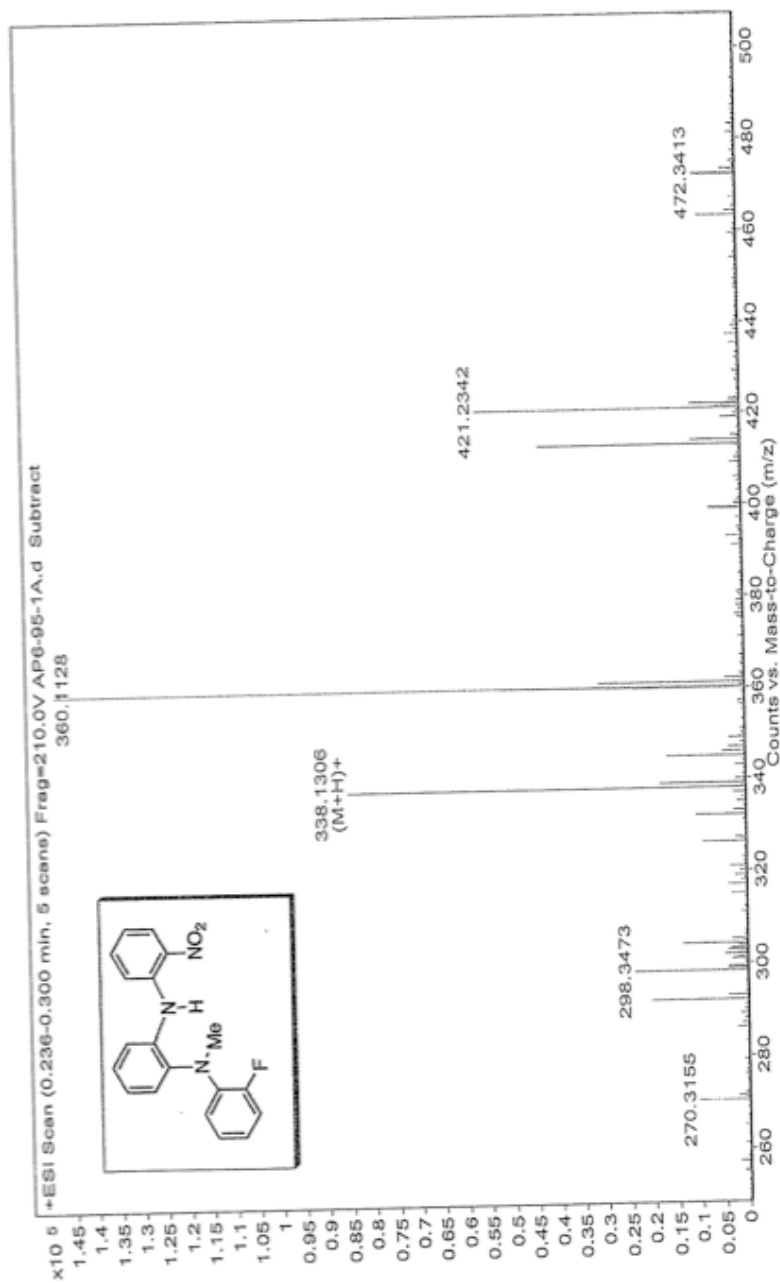




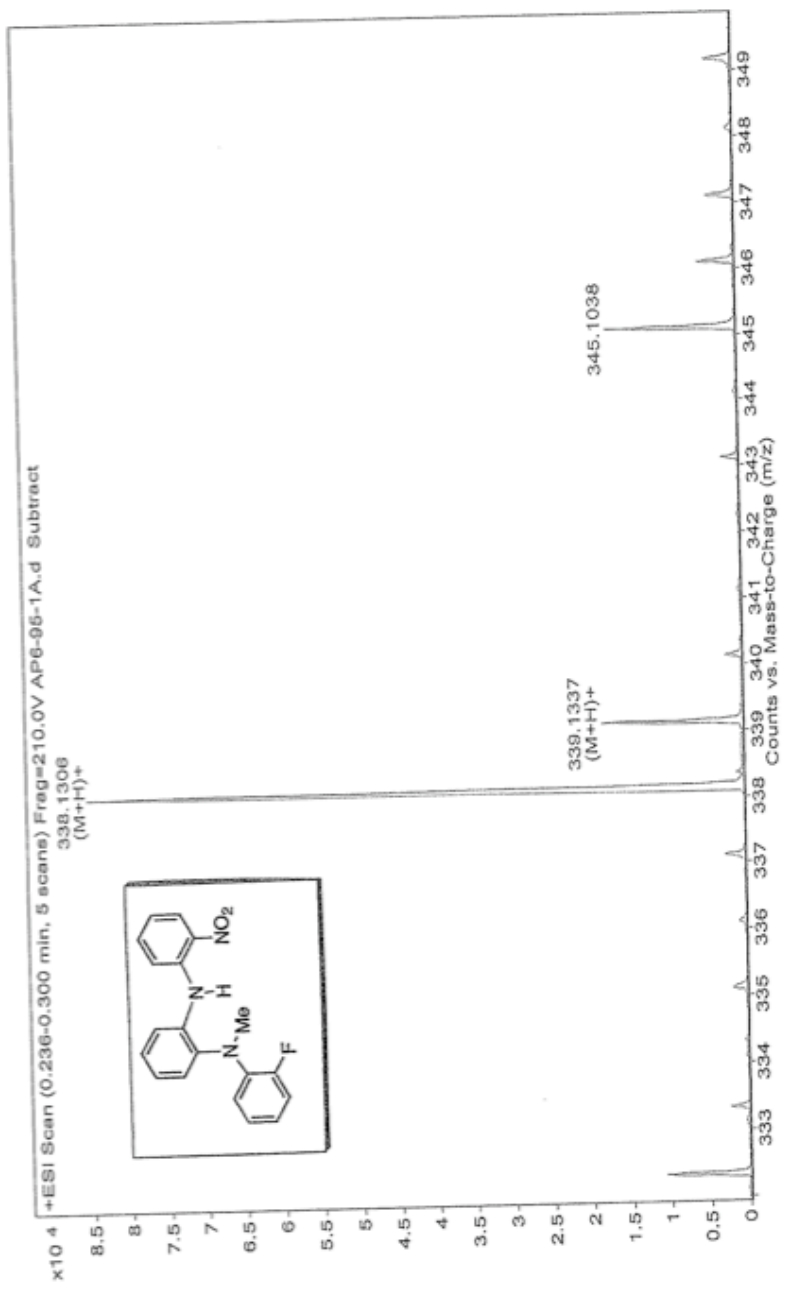
Sample Name AP6-95-1A
Inj Vol 2
Data Filename AP6-95-1A.d
Position InjPosition
ACQ Method
Instrument Name P1-A7
SampleType
Comment
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:45:02 AM

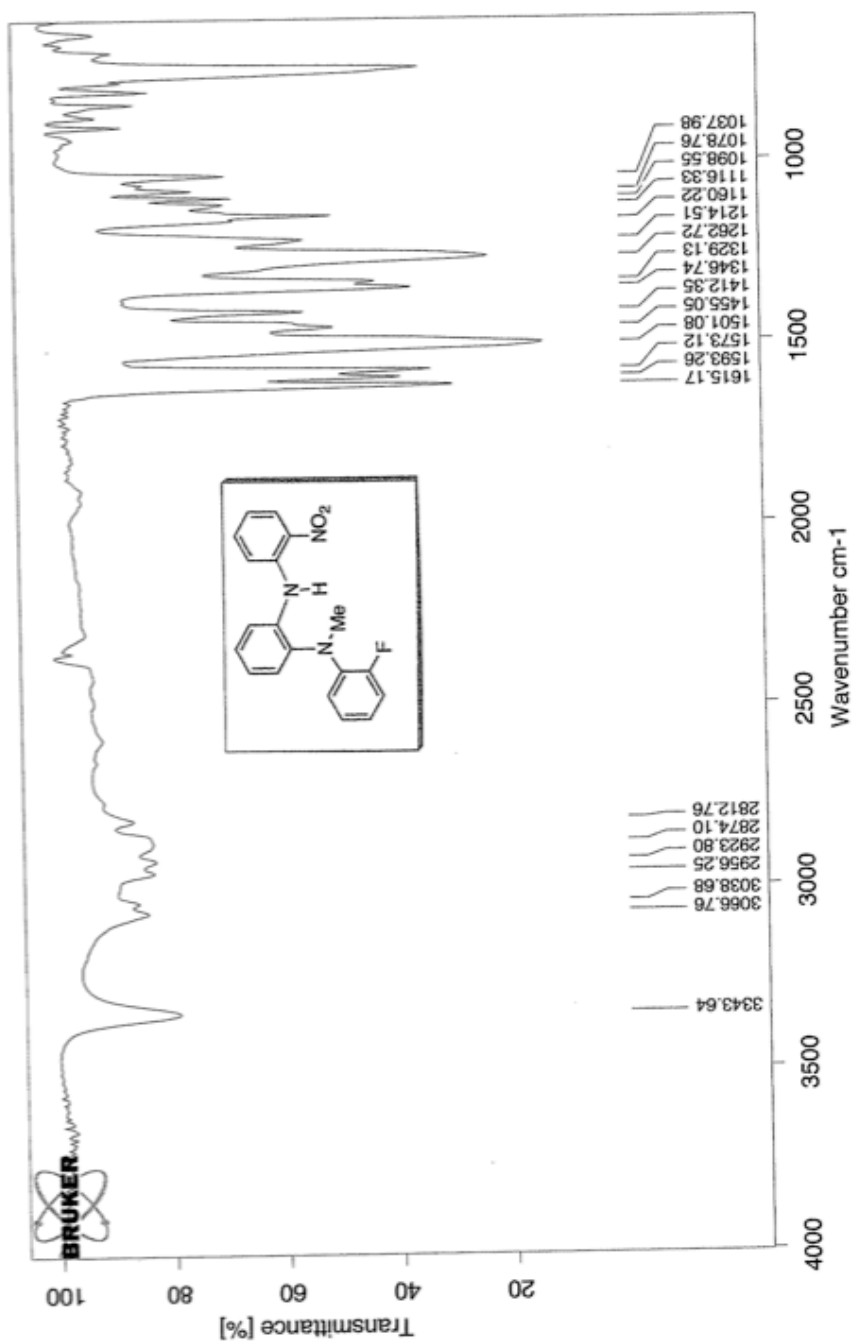


Sample Name AP6-95-1A
Inj Vol 2
Data Filename AP6-95-1A.d
Position InjPosition
ACQ Method
Instrument Name P1-A7
SampleType
Comment
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:45:02 AM



Sample Name	AP6-95-1A	Position	P1-A7	Instrument Name	Instrument 1	User Name
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status
Data Filename	AP6-95-1A.d	ACQ Method	ESI_ASI_Pos_03122009	Comment		Acquired Time
						Success
						6/25/2010 10:45:02 AM





07/06/2010

Instrument type and / or accessory

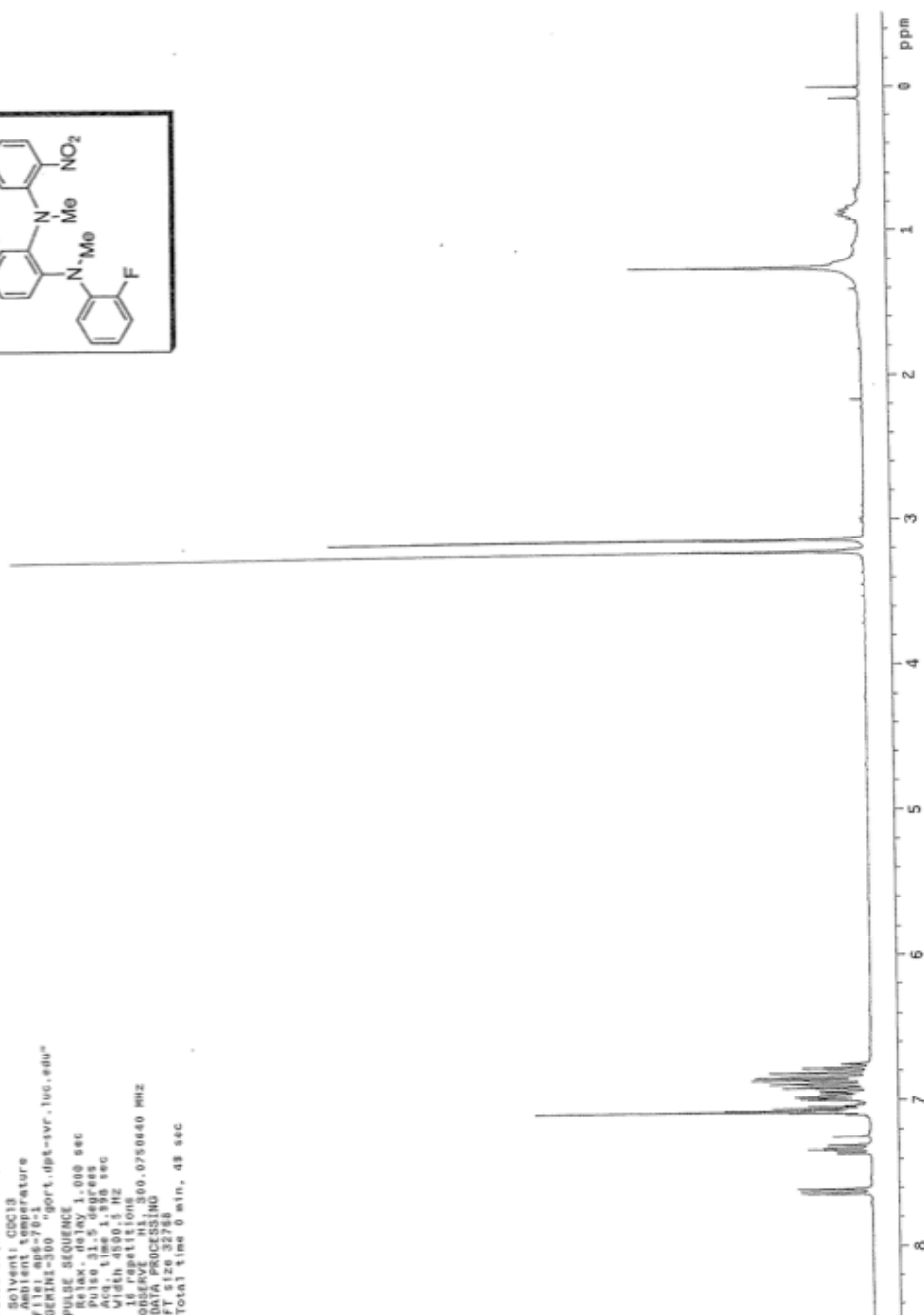
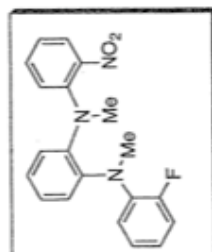
C:\Program Files\OPUS_65\Data\AP6 B.5

STANDARD 1H OBSERVE

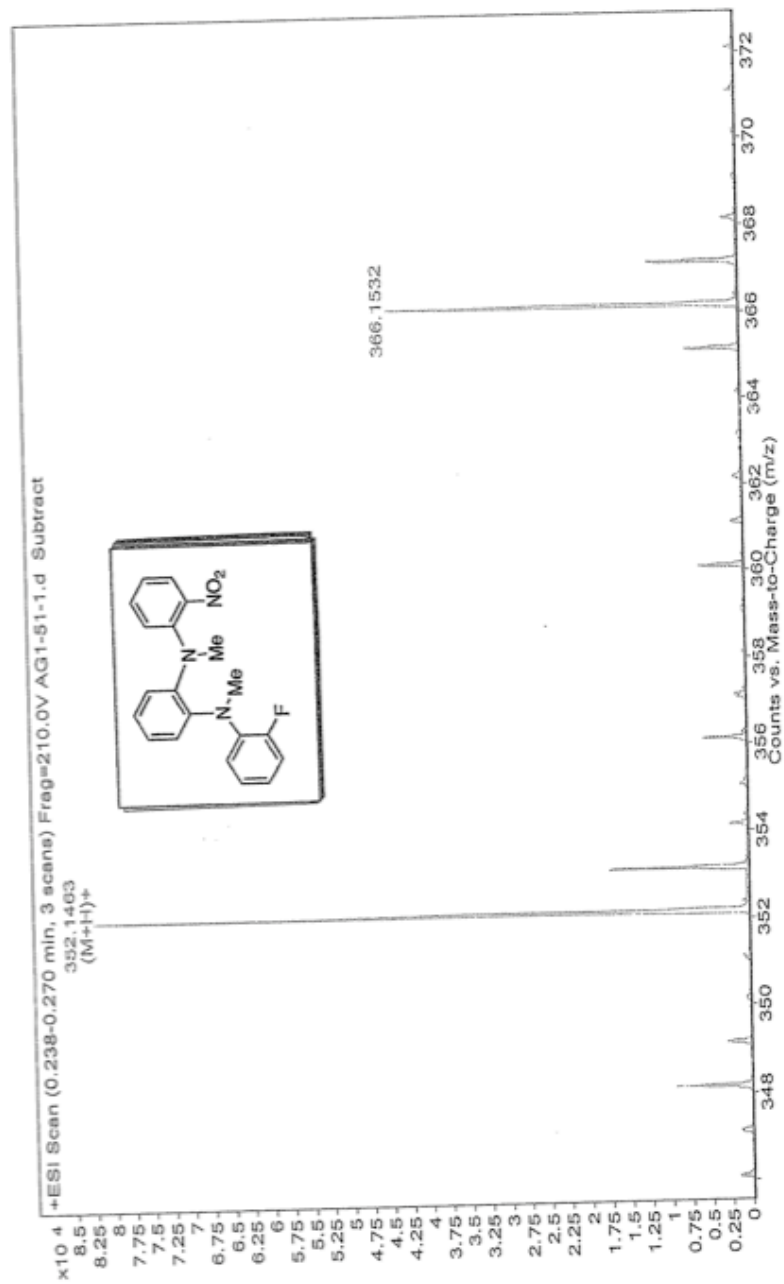
Pulse Sequence: s2pu1
 Solvent: CCl3
 Patient Temperature
 F100ms-70.1
 GEMINI-300 "gort.jpt-svf.tug.edu"

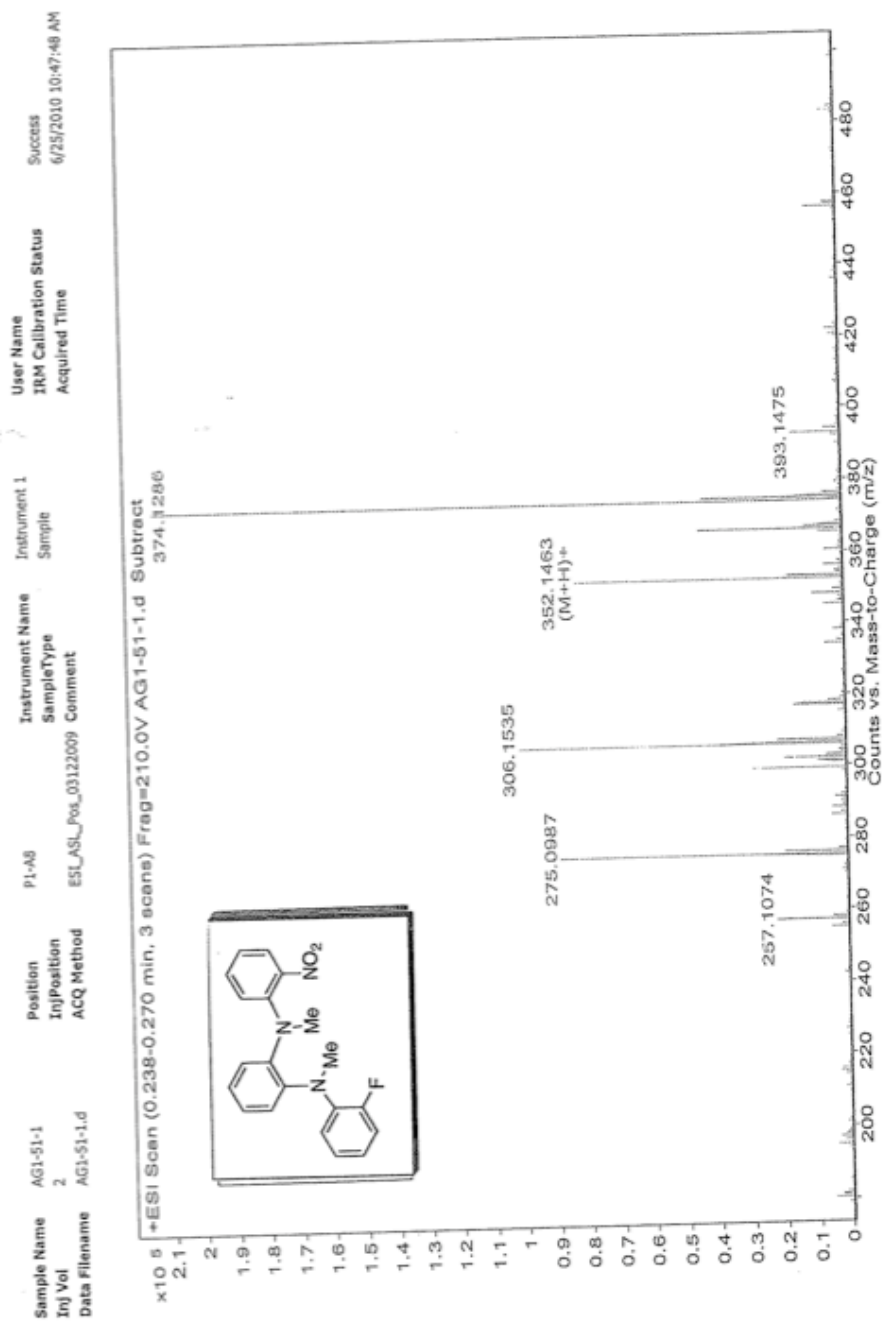
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 31.5 degrees
 Acq time 1.190 sec
 100 MHz
 10 repetitions

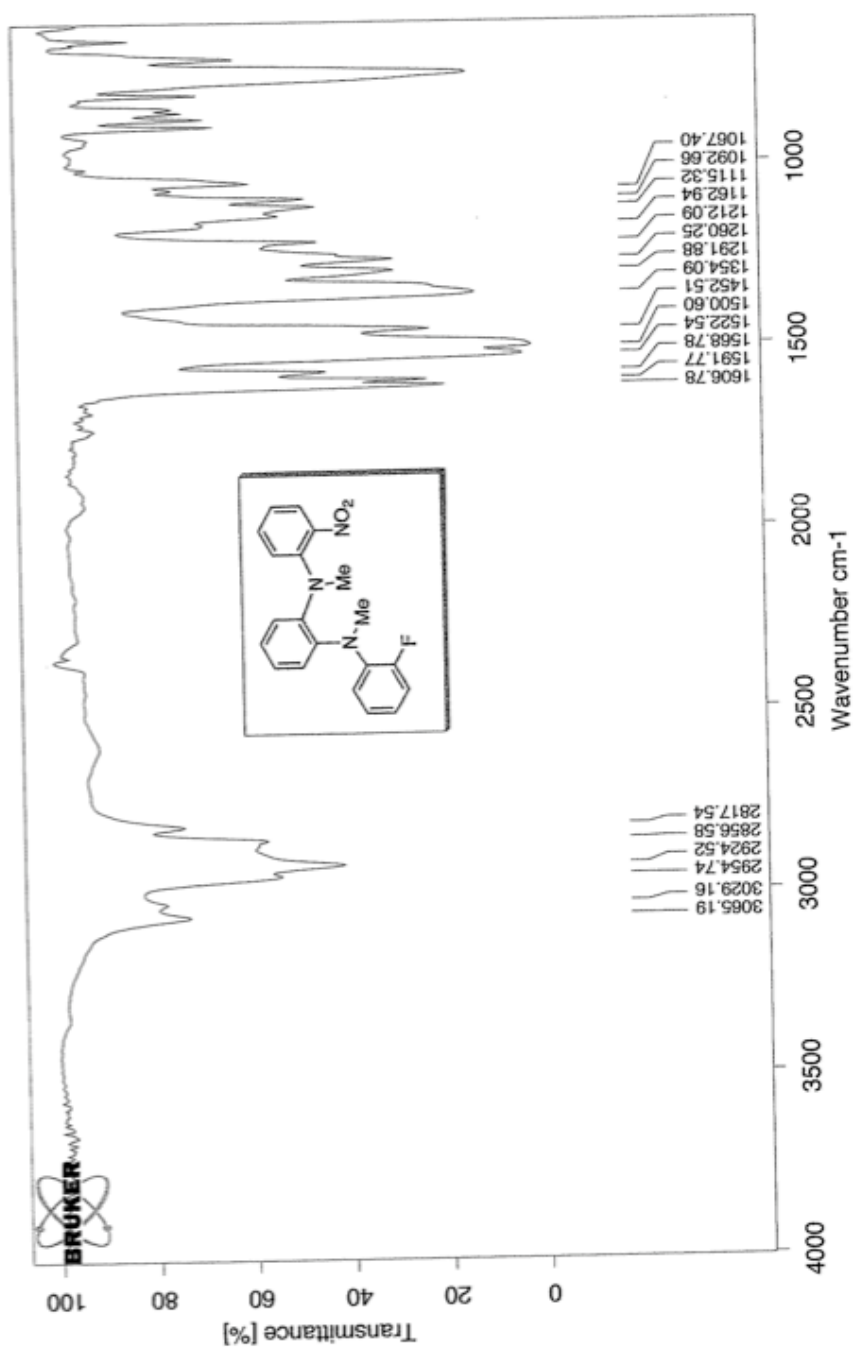
OBSERVE H1, 300.0750640 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min, 43 sec



Sample Name	AG1-S1-1	Position	P1-A8	Instrument Name	Instrument 1	User Name
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status
Data Filename	AG1-S1-1.d	ACQ Method	ESL_ASI_Pos_03122009	Comment		Acquired Time
						Success
						6/25/2010 10:47:48 AM







07/06/2010

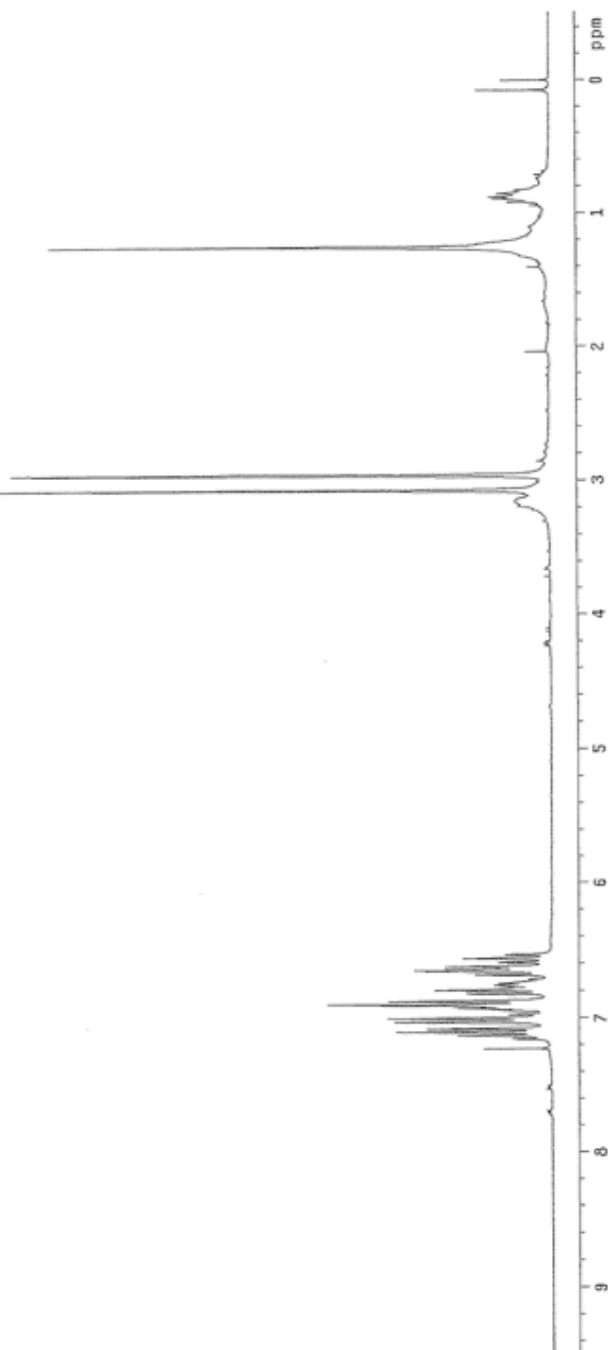
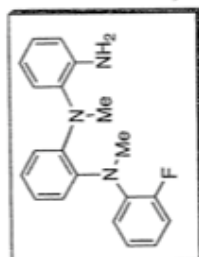
Instrument type and / or accessory

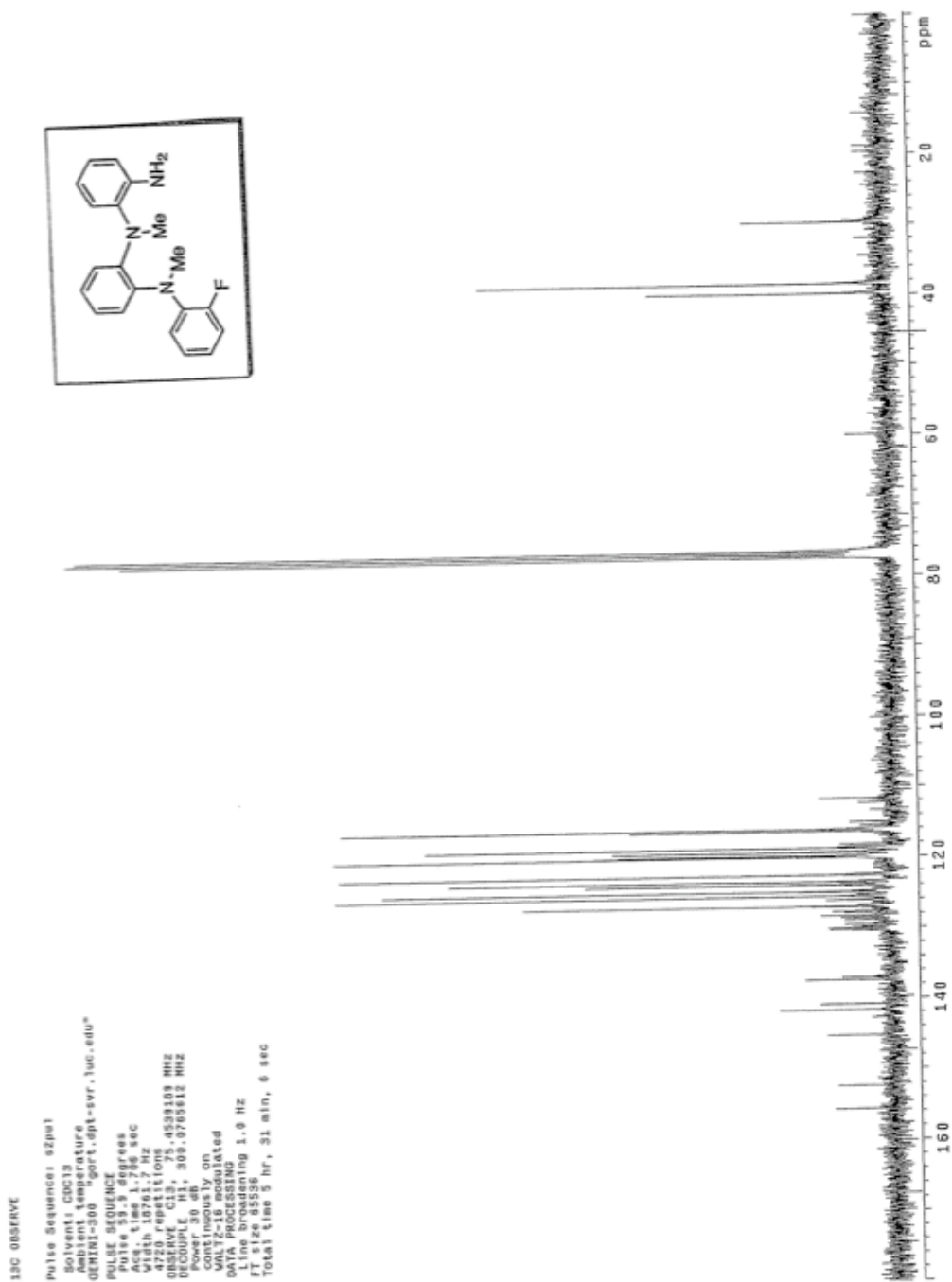
C:\Program Files\OPUS_65\Data\AP6 B.6

STANDARD IN OBSERVE

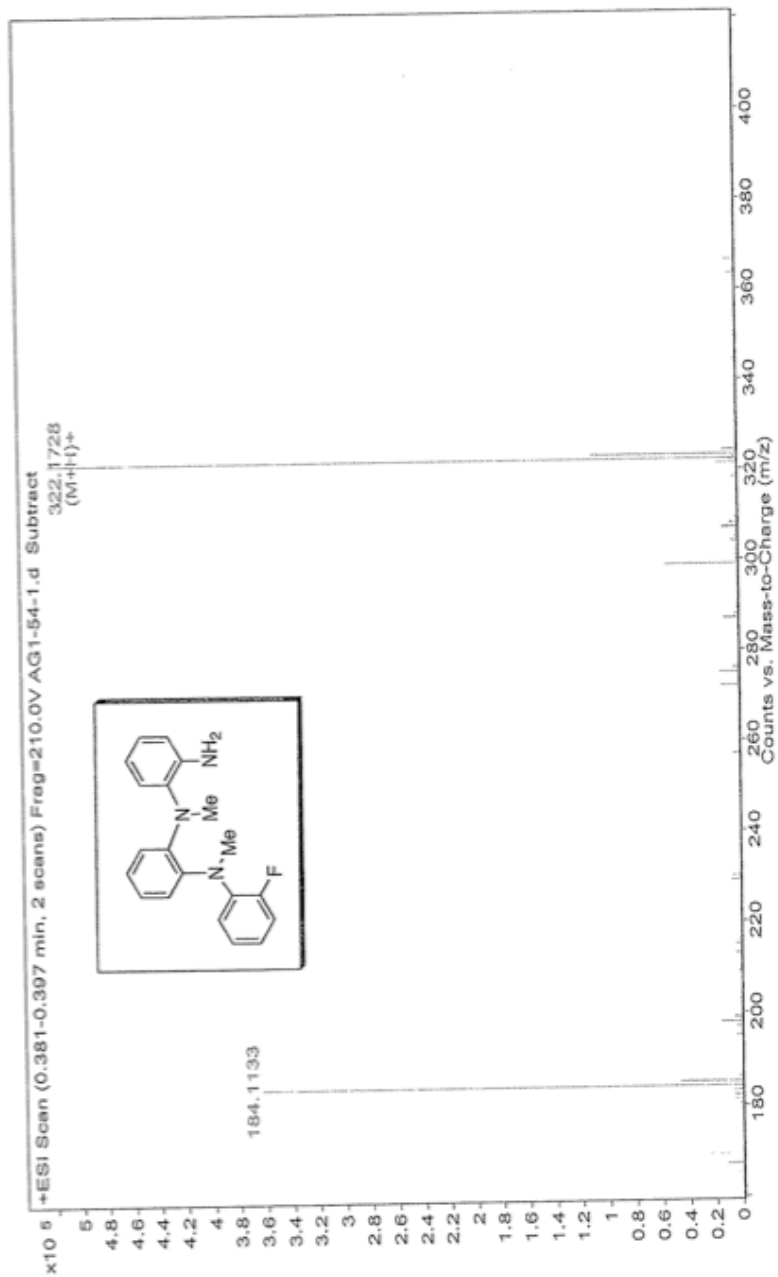
Pulse Sequence: szpul
Solvent: CDCl3
Ambient temperature
File: 466-67-1
GEMINI-500 -gort.dpt-svr.luc.edu

PULSE SEQUENCE
Relax: delay 1.000 sec
Acq: 32.199 sec
Acq: time 1.198 sec
Width 4500.5 Hz
Is repetitions
OBSERVED F1 size 32768
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec

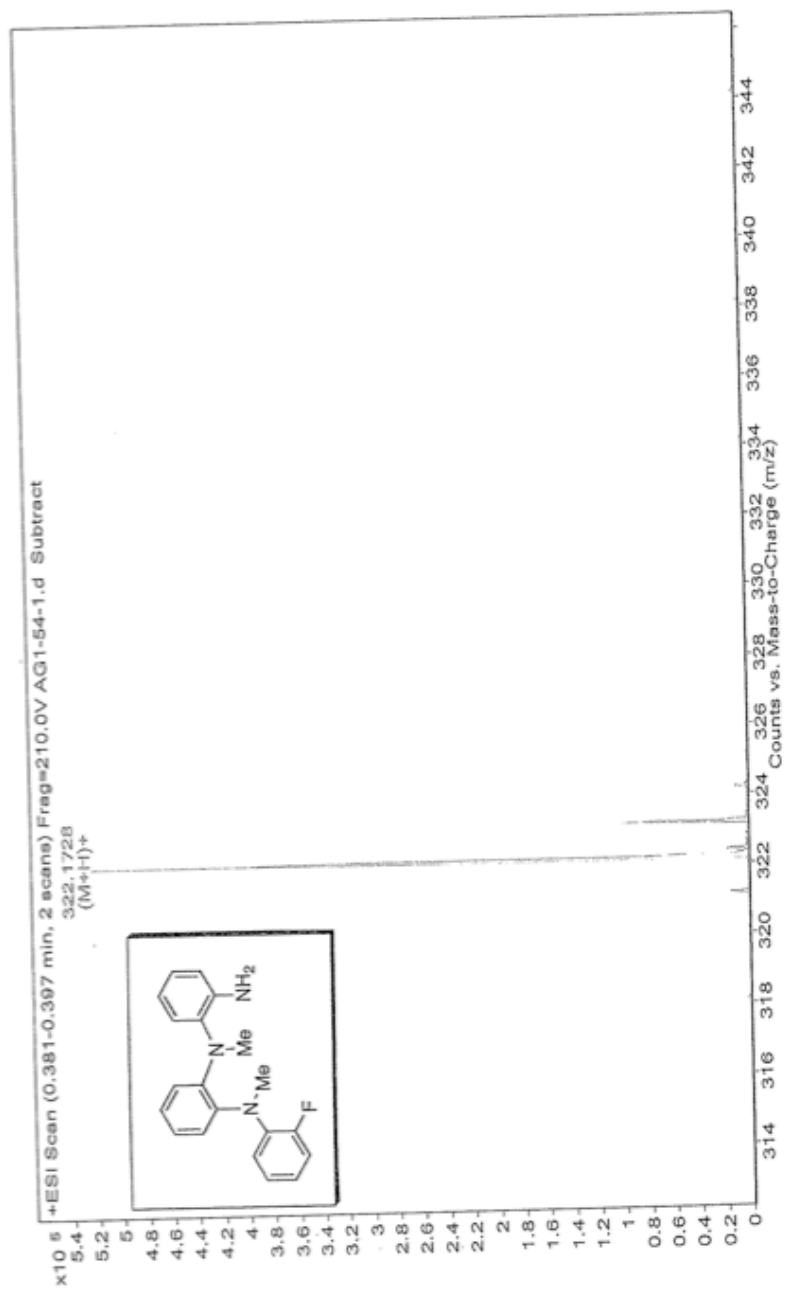


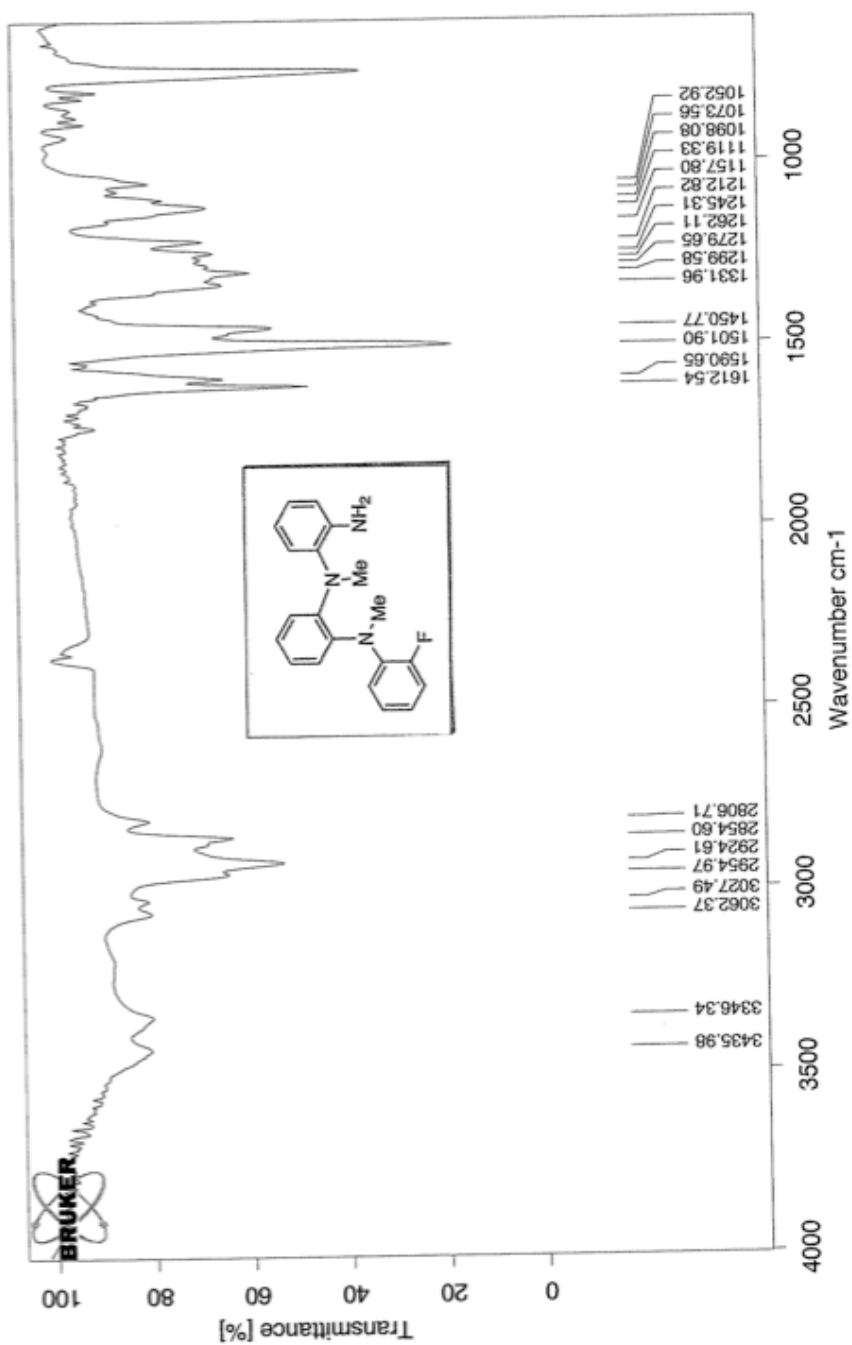


Sample Name	AG1-54-1	Position	PI-A9	Instrument Name	Instrument 1	User Name
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status
Data Filename	AG1-54-1.d	ACQ Method	ESI_ASL_Pos_03122009	Comment		Acquired Time
						Success
						6/25/2010 10:50:27 AM



Sample Name	AG1-54-1	Position	P1-A9	Instrument Name	Instrument 1	User Name
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status
Data Filename	AG1-54-1.d	ACQ Method	ESI_AS_Pos_03122009	Comment		Acquired Time
						Success
						6/25/2010 10:50:27 AM





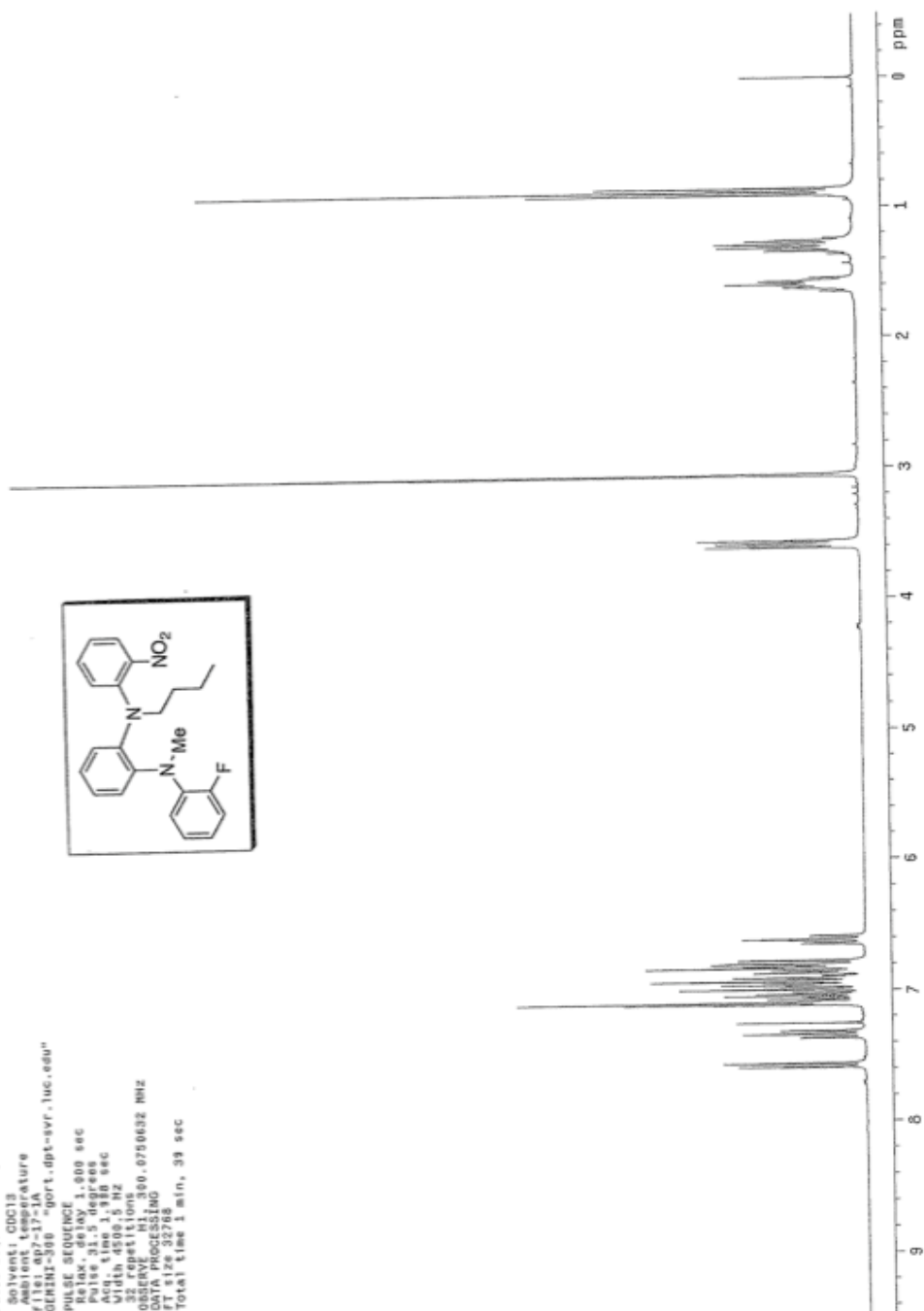
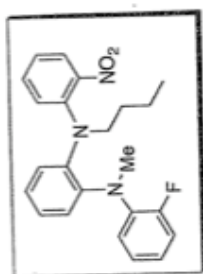
07/06/2010

Instrument type and / or accessory

C:\Program Files\OPUS_65\Data\AP6 B.8

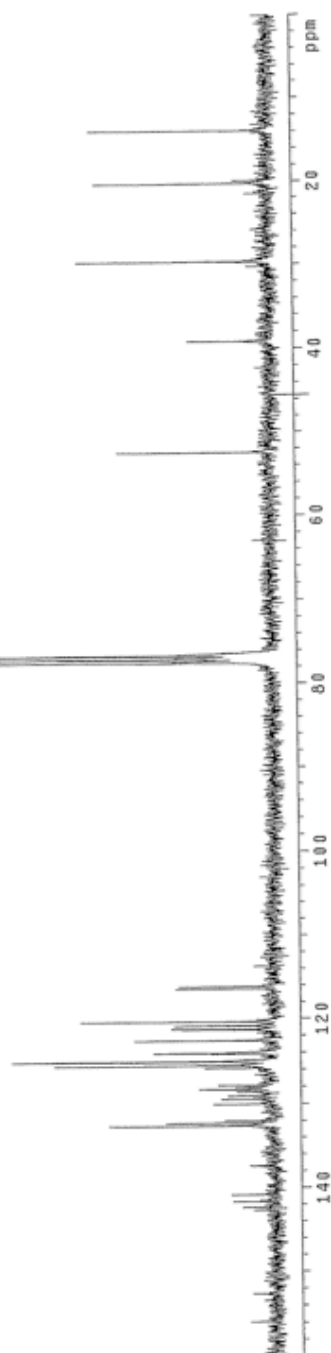
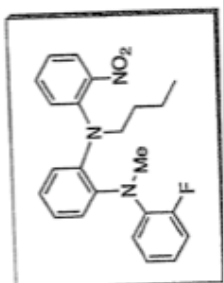
STANDARD 1H OBSERVE

Pulse Sequence: zgpg30
Solvent: CDCl3
Acq. temperature: 300.2 K
F1: 400.137-137.1A
GEMINI-300 "gort.dpt-svr.luc.edu"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 1.980 sec
Sweep width 10000 Hz
32 acquisitions
OBSERVE M1: 300.0750632 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

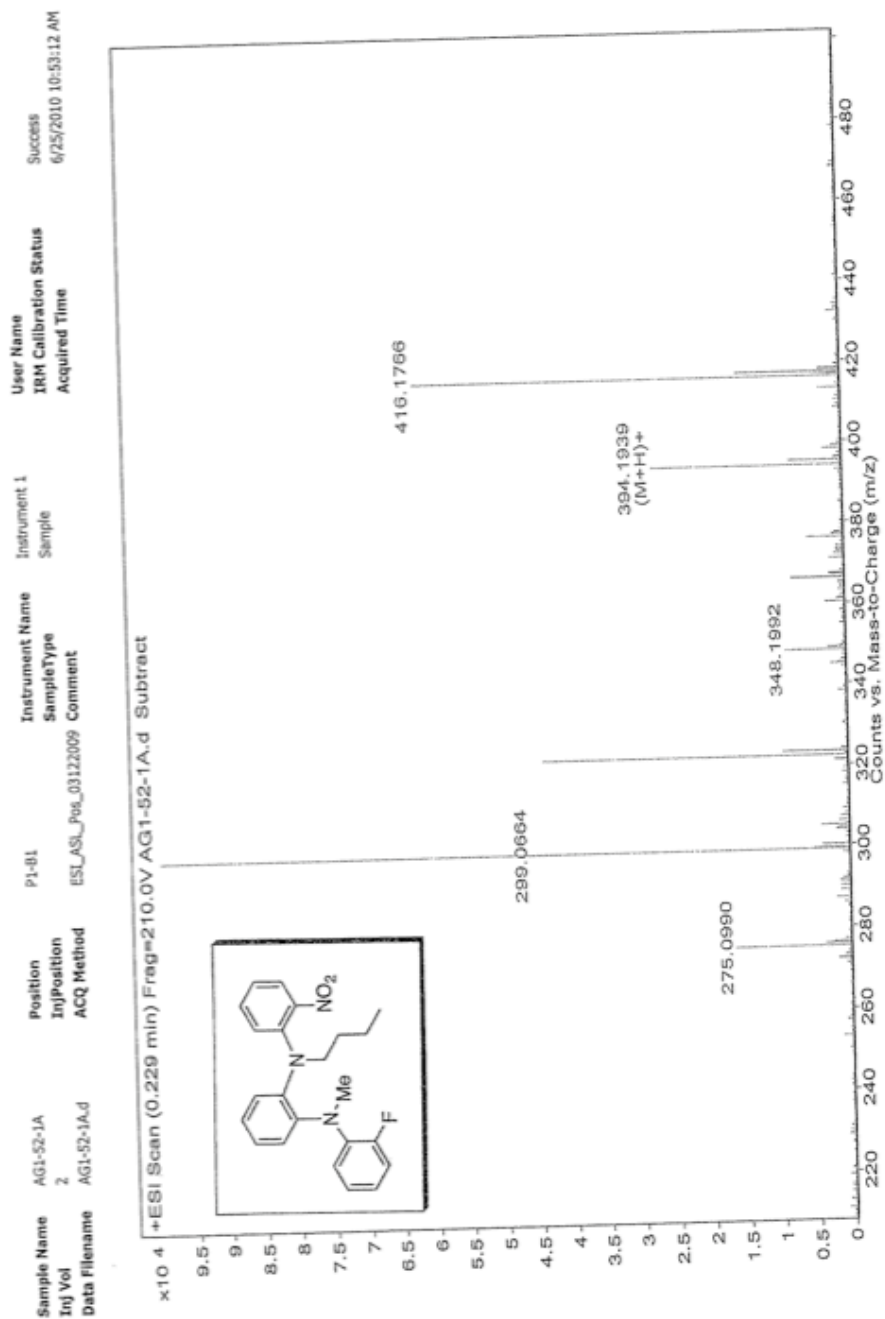


13C OBSERVE

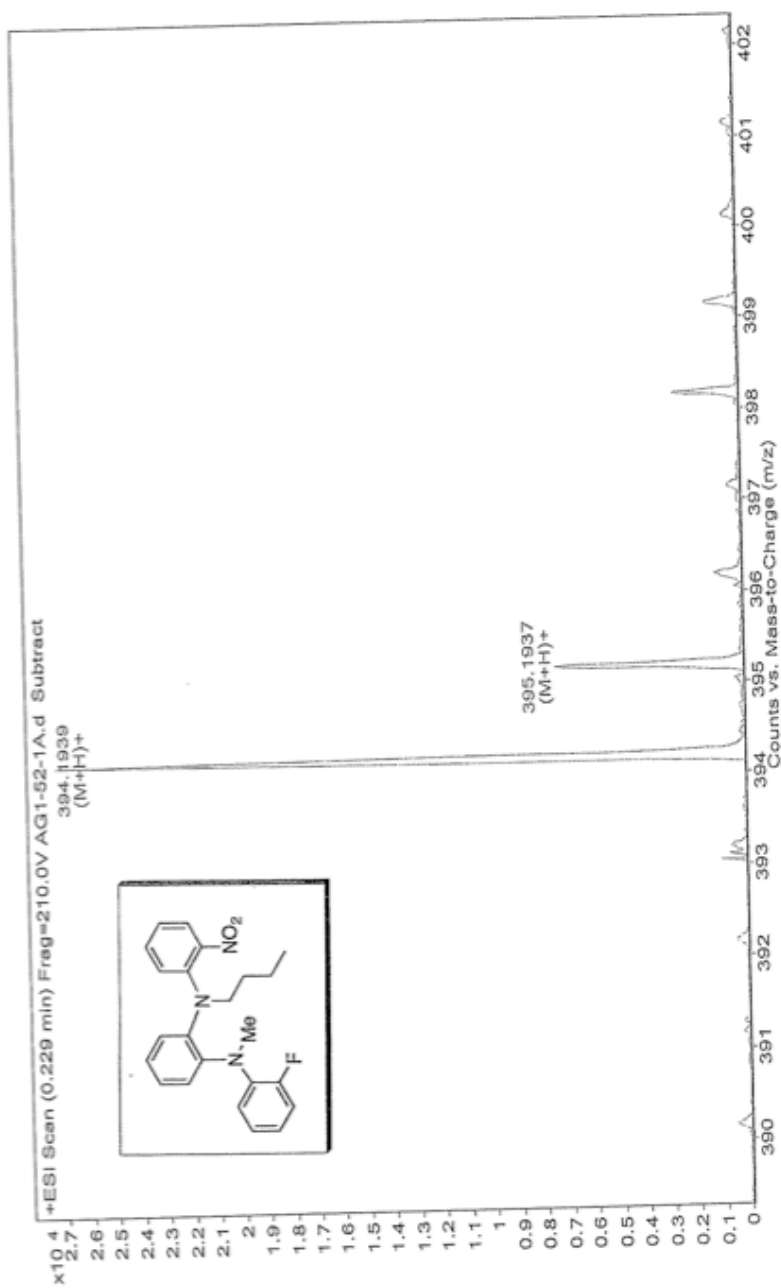
Pulse Sequence: zgpg30
 Solvent: CDCl3
 Ambient temperature
 OPM1-360 -gort-ept-svr.luc.edu
 PULSE SEQUENCE
 zgpg30
 Width 15761.7 Hz
 Acquisition time 1.266 sec
 16000 repetitions
 OBSERVE CH 2 - 453108 MHz
 RECORD CH 1 - 350.076512 MHz
 Power 30 dB
 continuously on
 VOLT2-16 modulated
 DATA PROCESSING
 F1 size 65536
 FT size 65536
 Total time 5 hr, 31 min, 6 sec



Am1-52-1 carbon



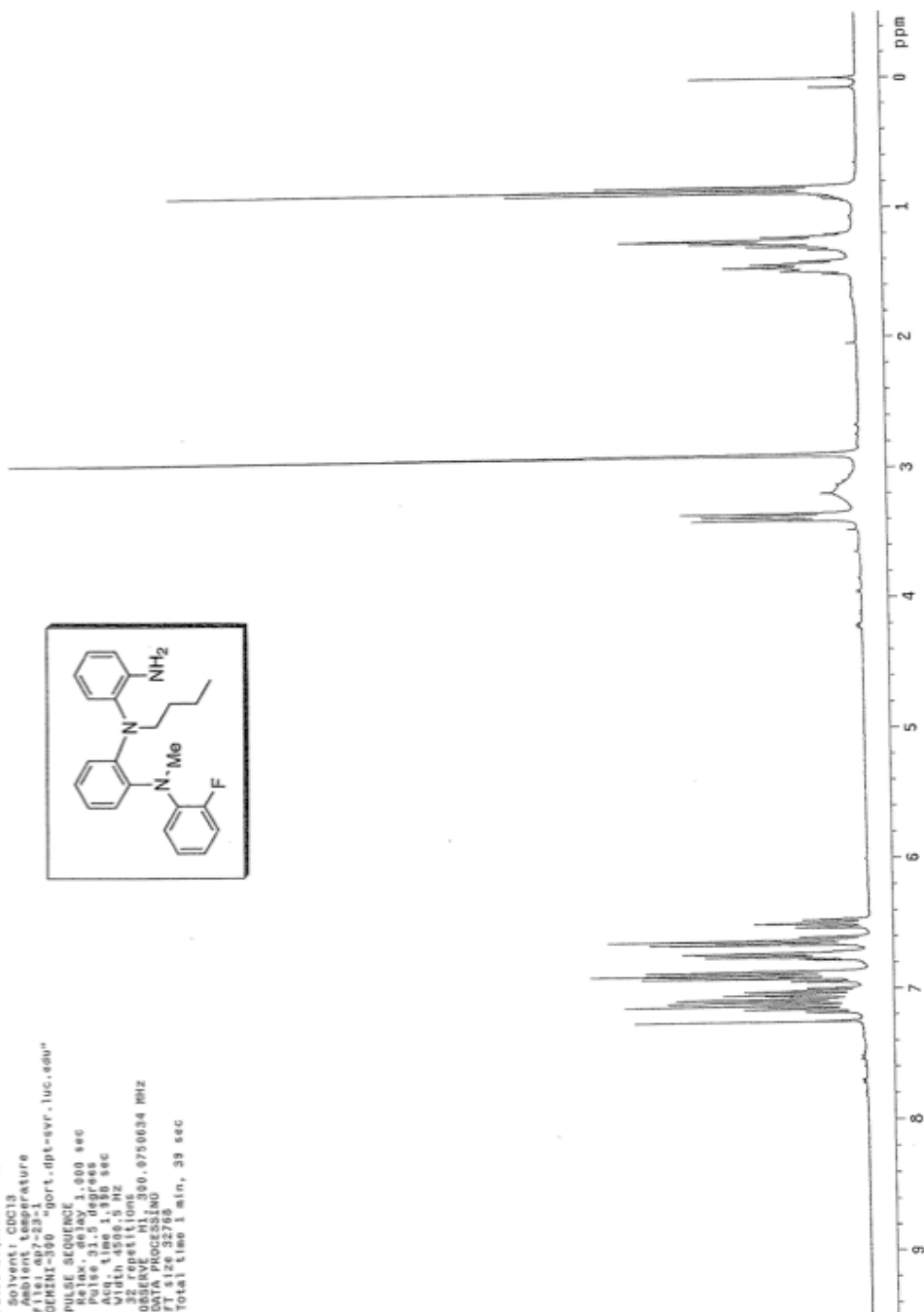
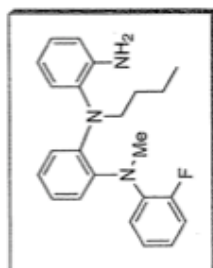
Sample Name AG1-52-1A
Inj Vol 2
Data Filename AG1-52-1A.d
Position InjPosition
ACQ Method
PI-B1
Instrument Name
SampleType
Sample Comment
ESL_ASI_Pos_03122009
Instrument 1
Sample
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 10:53:12 AM



STANDARD IN OBSERVE

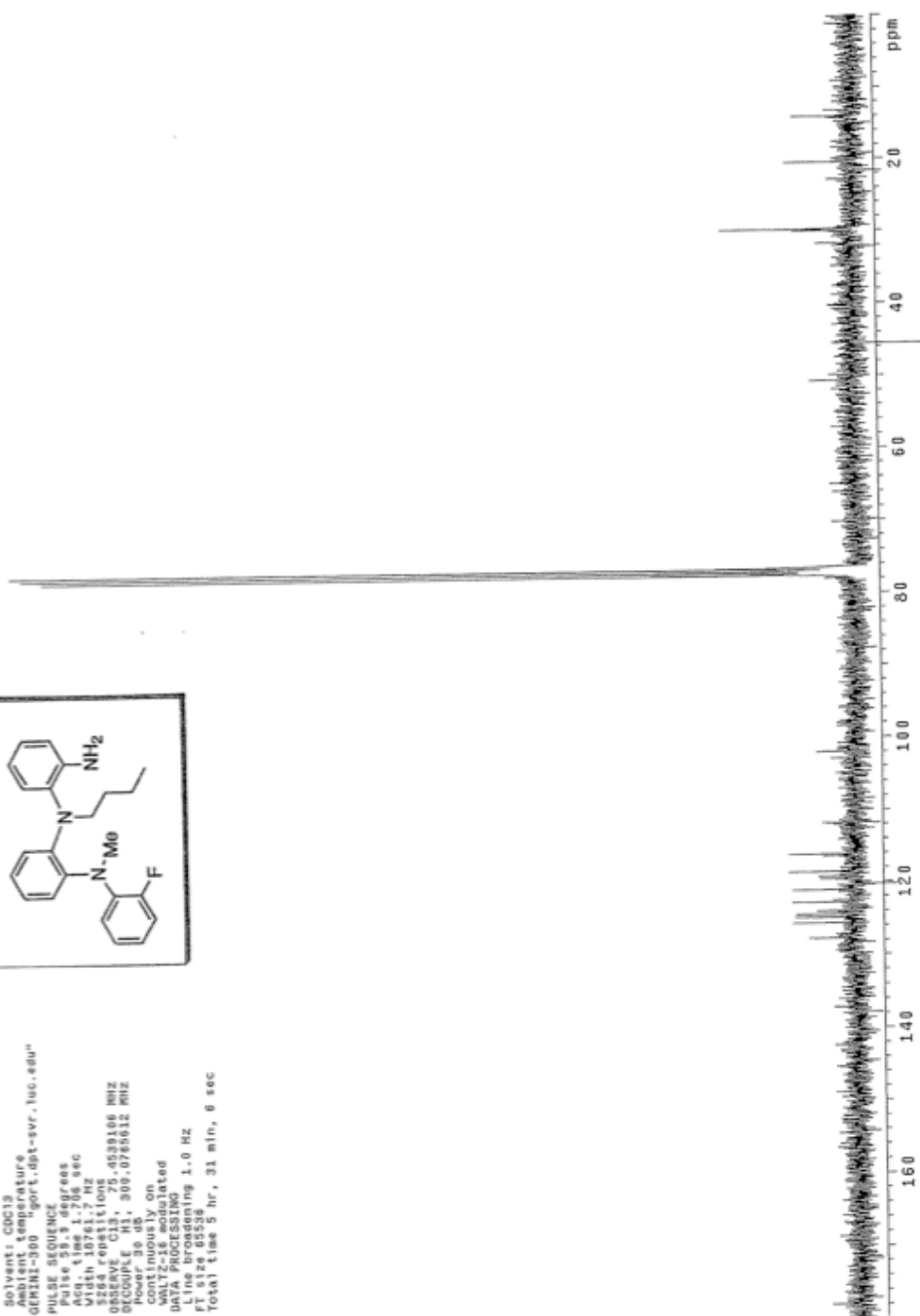
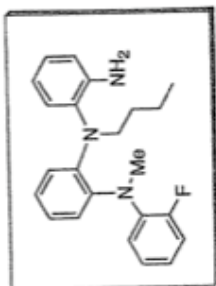
Pulse Sequence: s2pu1
Solvent: CDCl3
Acquisition Date: 07-23-11
File: 07-23-11
GEMIN-500 "gort.dpt-svr, luc.edu"

PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 31.5 degree
Acq. time 0.000 sec
SOLVENT
32 repetitions
OBSERVE H1, 300.0750034 MHz
DATA PROCESSING
F1 size 32768
Total time 1 min, 39 sec



13C OBSERVE

Pulse Sequence: szpul
 Solvent: CDCl3
 Ambient temperature
 GERINI-300 "gort.dgt-svr.tug.edu"
 PULSE SEQUENCE
 Pulse 38.9 degrees
 Width 18761.7 Hz
 Width 18761.7 Hz
 5284 repetitions
 OBSERVE C13, 75.4535166 MHz
 DECOUPLE H1, 300.0760612 MHz
 Continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 F1 us Broadening 1.0 Hz
 FT us 4558
 Total time 5 hr, 31 min, 6 sec



Sample Name AG1-52-1Red
Inj Vol 2
Data Filename AG1-52-1Red.d

Position
InjPosition
ACQ Method

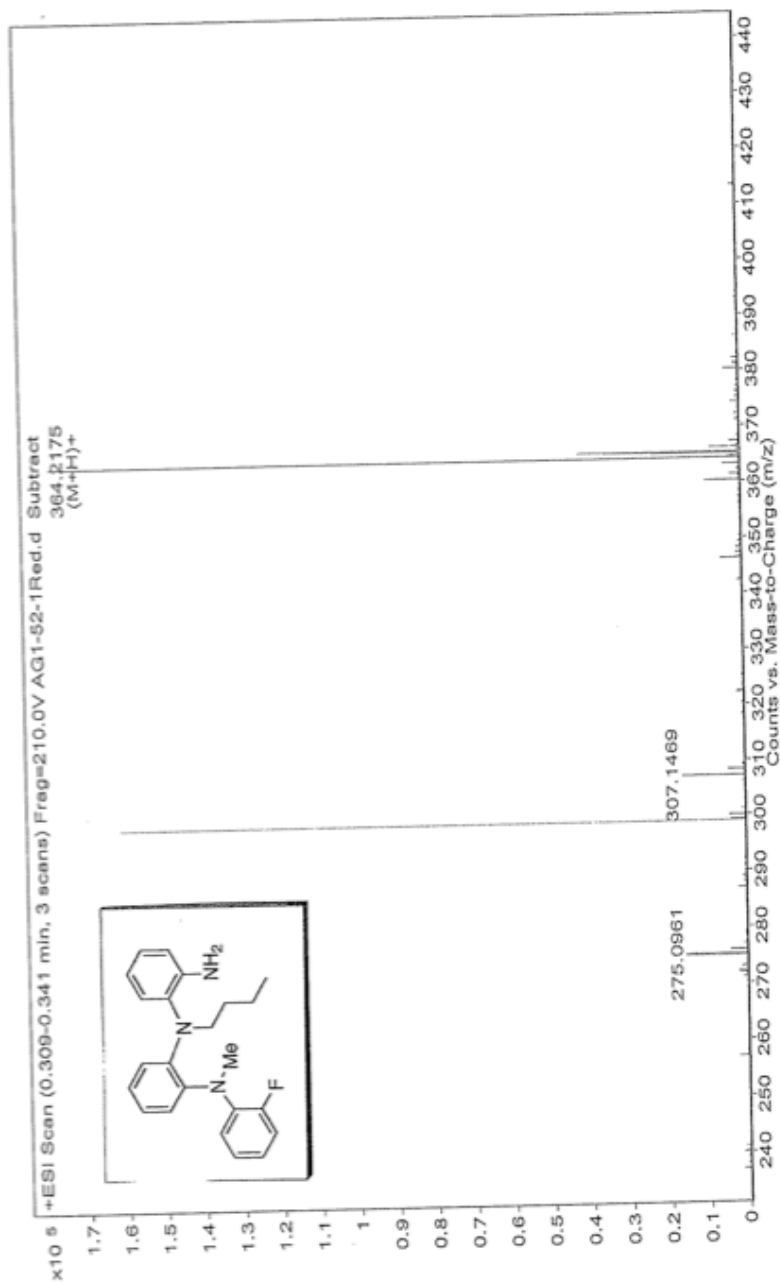
P1-82
ESL_AS_Pos_03122009 Comment

Instrument Name
SampleType
Sample

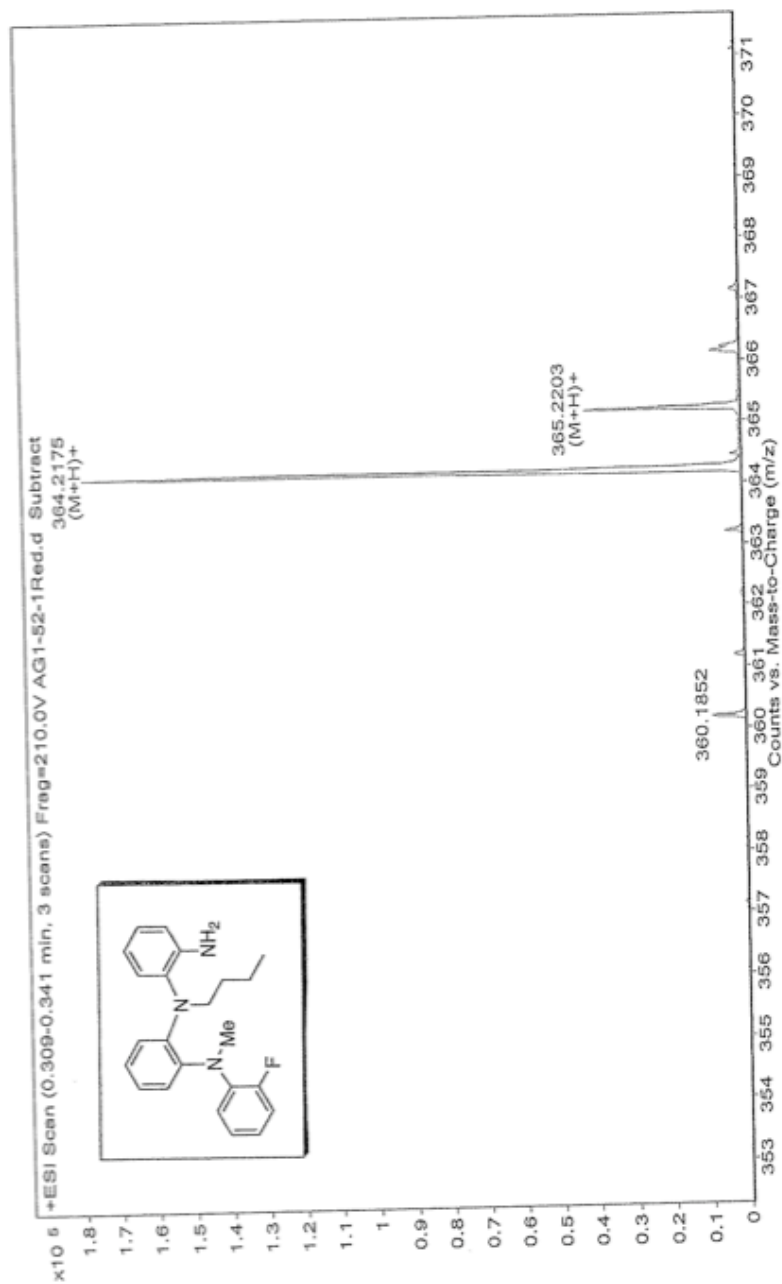
Instrument 1
Sample

User Name
IRM Calibration Status
Acquired Time

Success
6/25/2010 10:55:52 AM

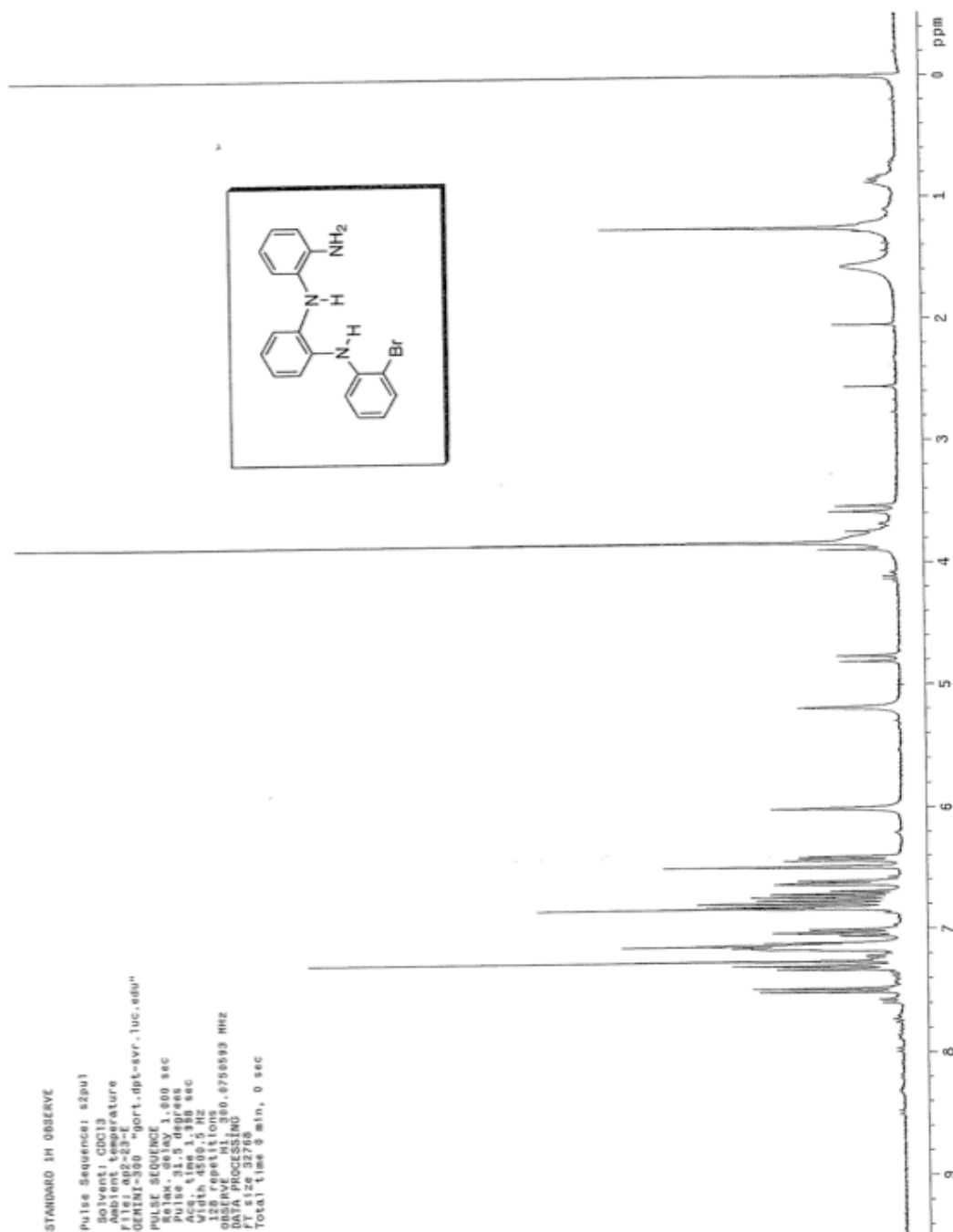
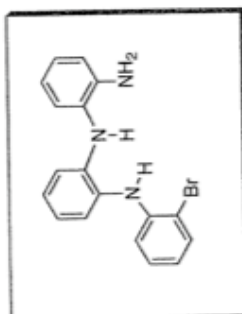


Sample Name AG1-52-1Red Instrument Name P1-82 User Name
Inj Vol 2 Instrument 1 Sample ILM Calibration Status Success
Data Filename AG1-52-1Red.d ESI_ASI_Pos_03122009 Comment Acquired Time 6/25/2010 10:55:52 AM

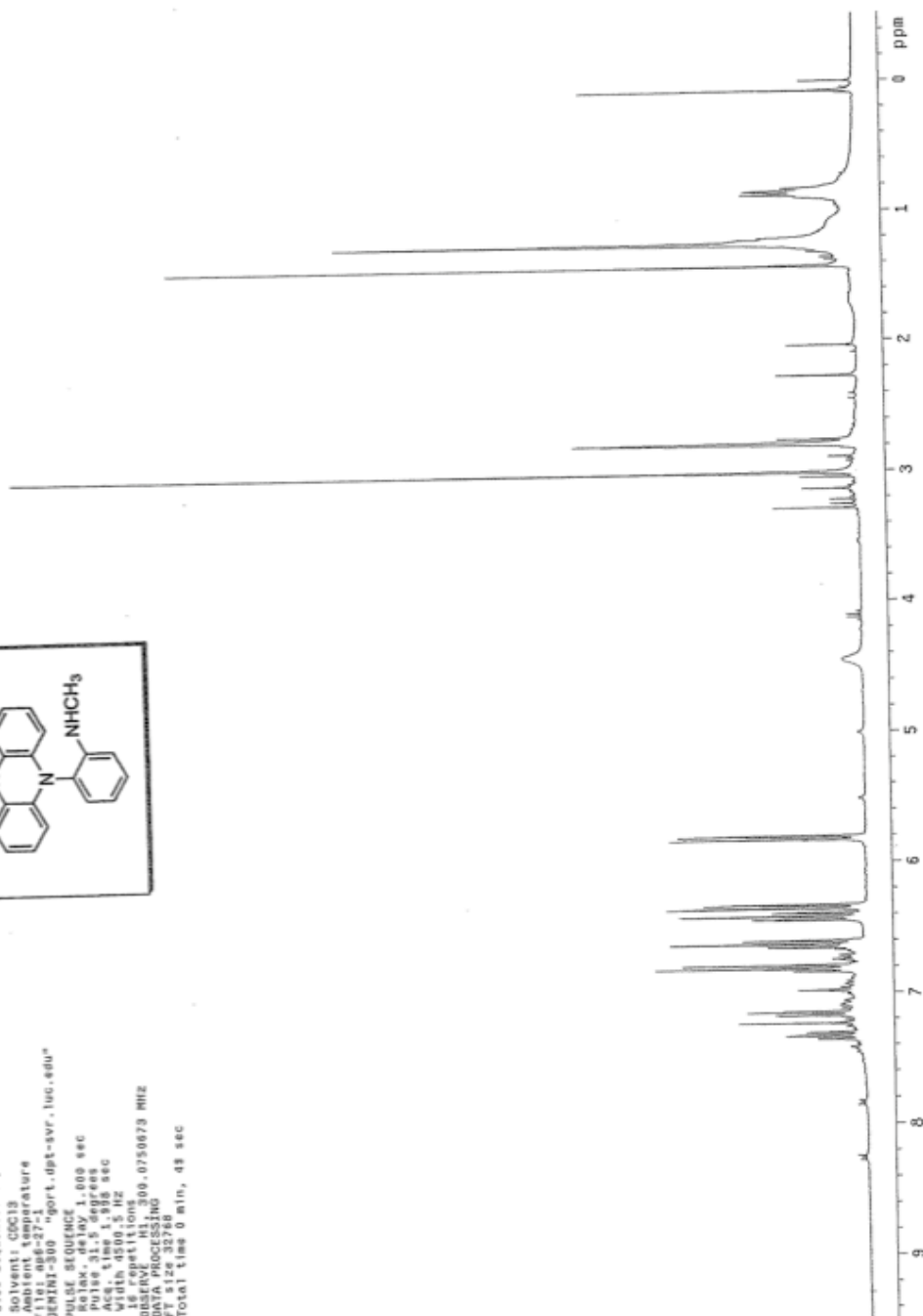
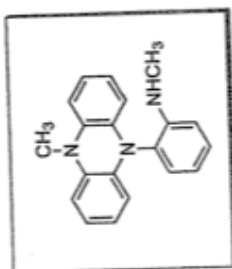


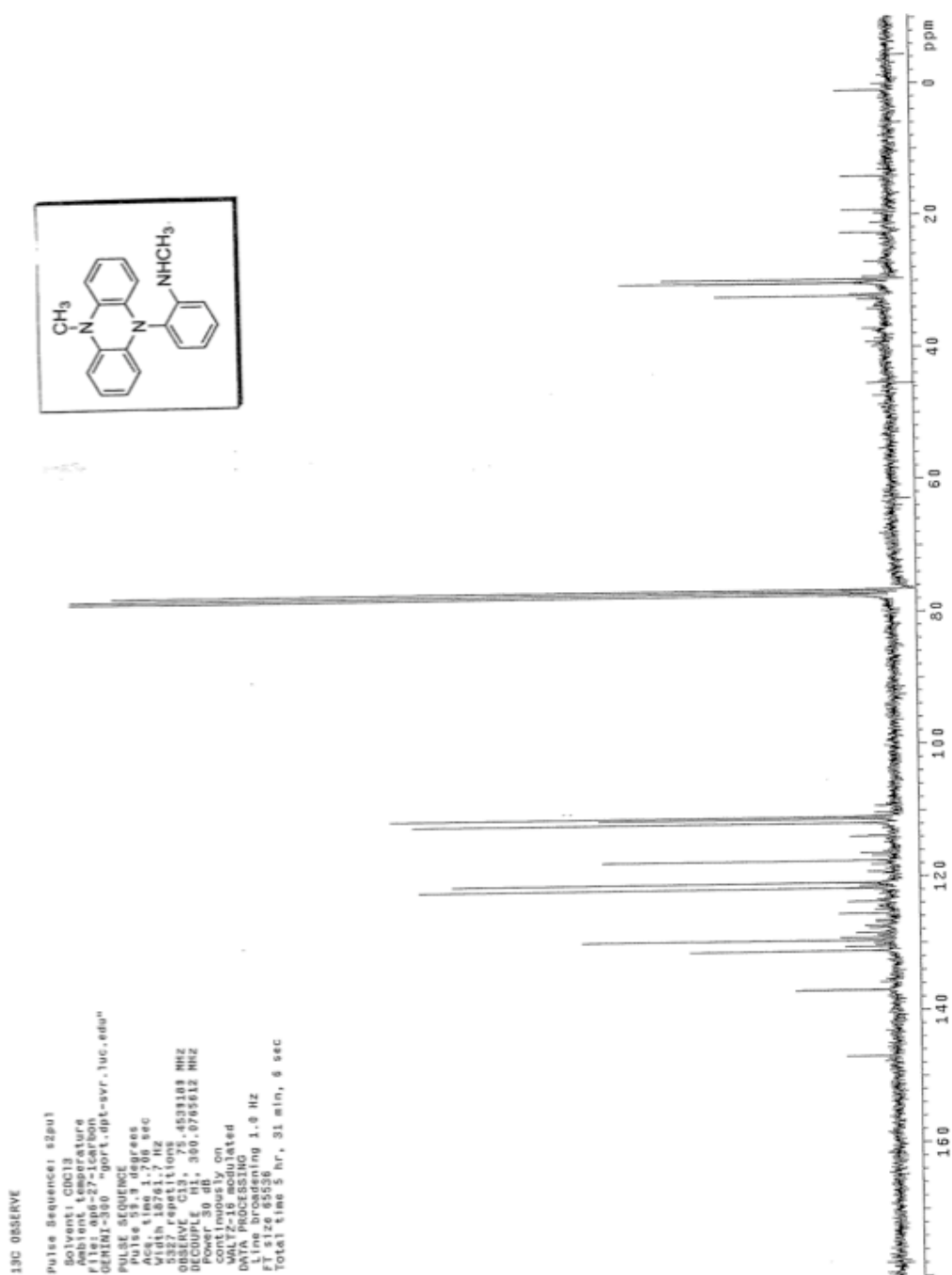
STANDARD IN OBSERVE

Pulse Sequence: s2pu1
Solvent: CDCl3
Acquisition Temperature
File: ap2-13-E
GENTAI-350 "gort.dpt-svf.luc.edu"
PULSE SEQUENCE
Relax: delay 1.000 sec
Pulse 31.5 degrees
Acq. time 1.980 sec
128 repetitions
OBSERVE H1, 320.6750593 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 0 sec

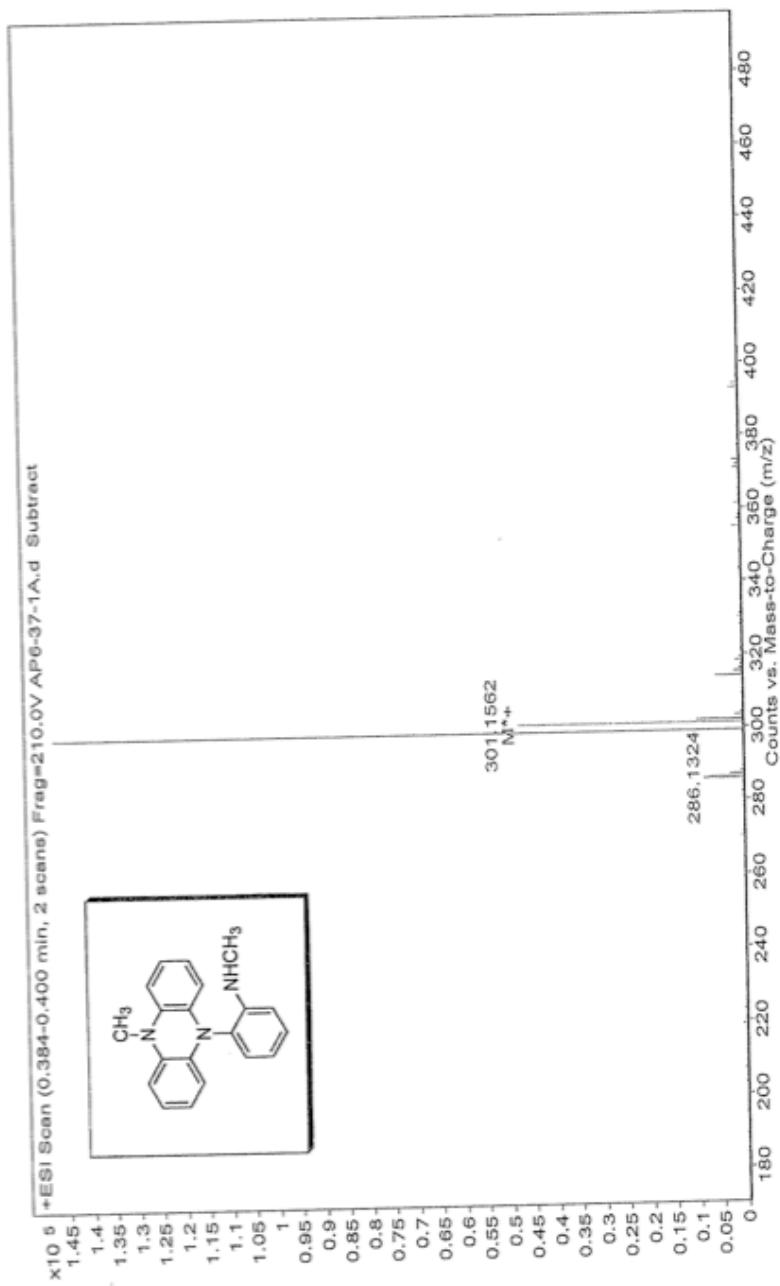


STANDARD 1H OBSERVE
Pulse Sequence: s2pu1
Solvent: CDCl3
Ambient temperature
F1: 400.136275 MHz
QNP1H1-200.136275 MHz
QNP1H1-200.136275 MHz
PULSE SEQUENCE
Pulse delay: 1.000 sec
Pulse: 31.5 degrees
Acq. time: 1.998 sec
Width: 4500.0 Hz
Sensitivity: 1.000000
OBSERVE H1: 300.0750673 MHz
DATA PROCESSING
FT size: 32768
Total time: 0 min, 43 sec

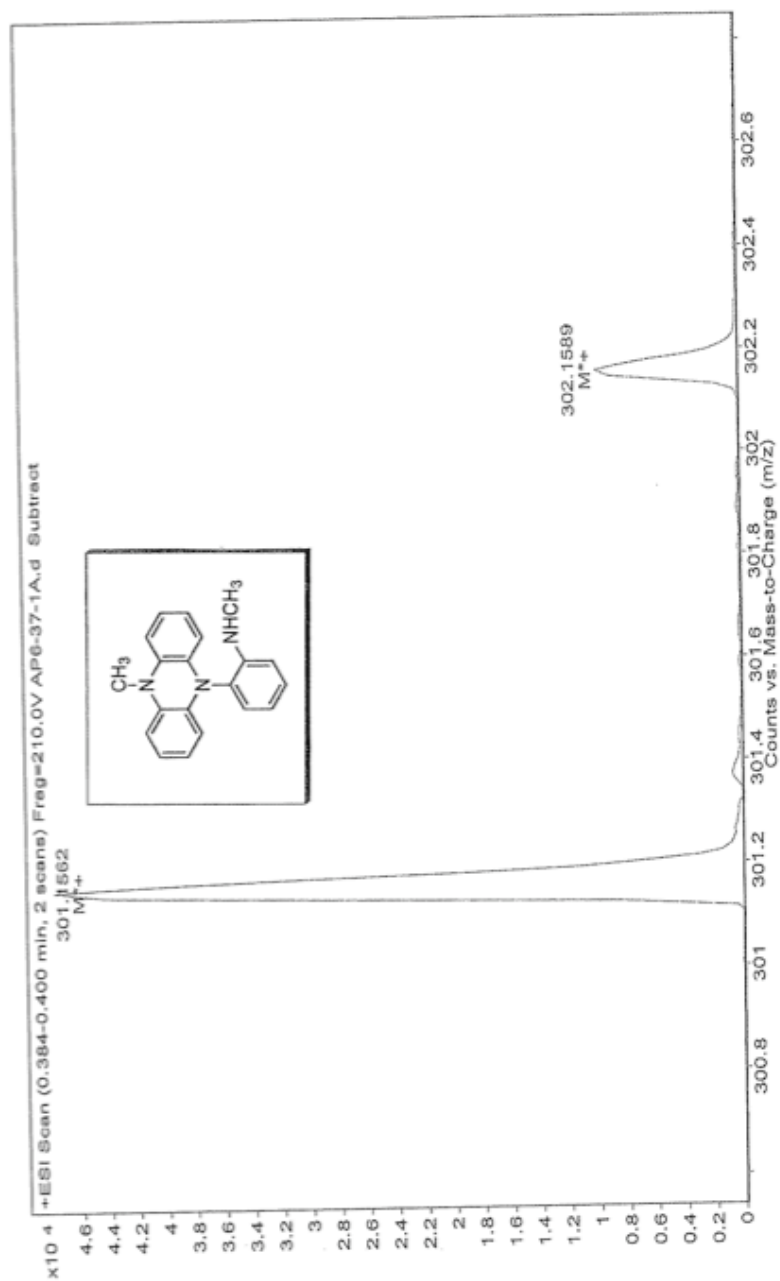




Sample Name	AP6-37-1A	Position	P1-83	Instrument Name	Instrument 1	User Name	Success
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	6/25/2010 11:43:47 AM
Data Filename	AP6-37-1A.d	ACQ Method	ESL_AS_Los_03122009	Comment		Acquired Time	

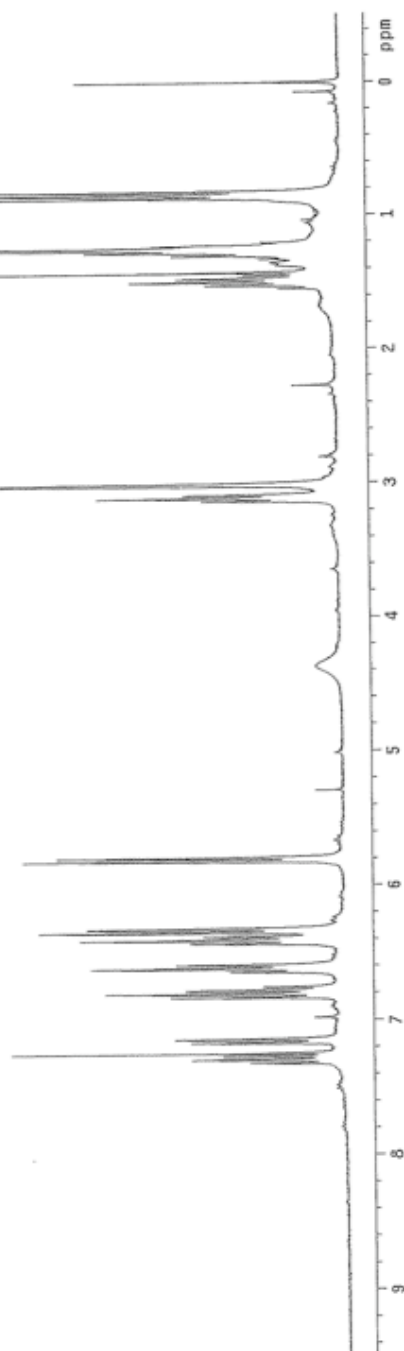
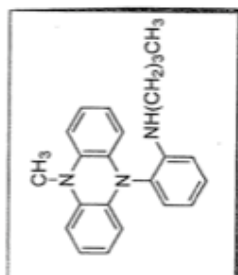


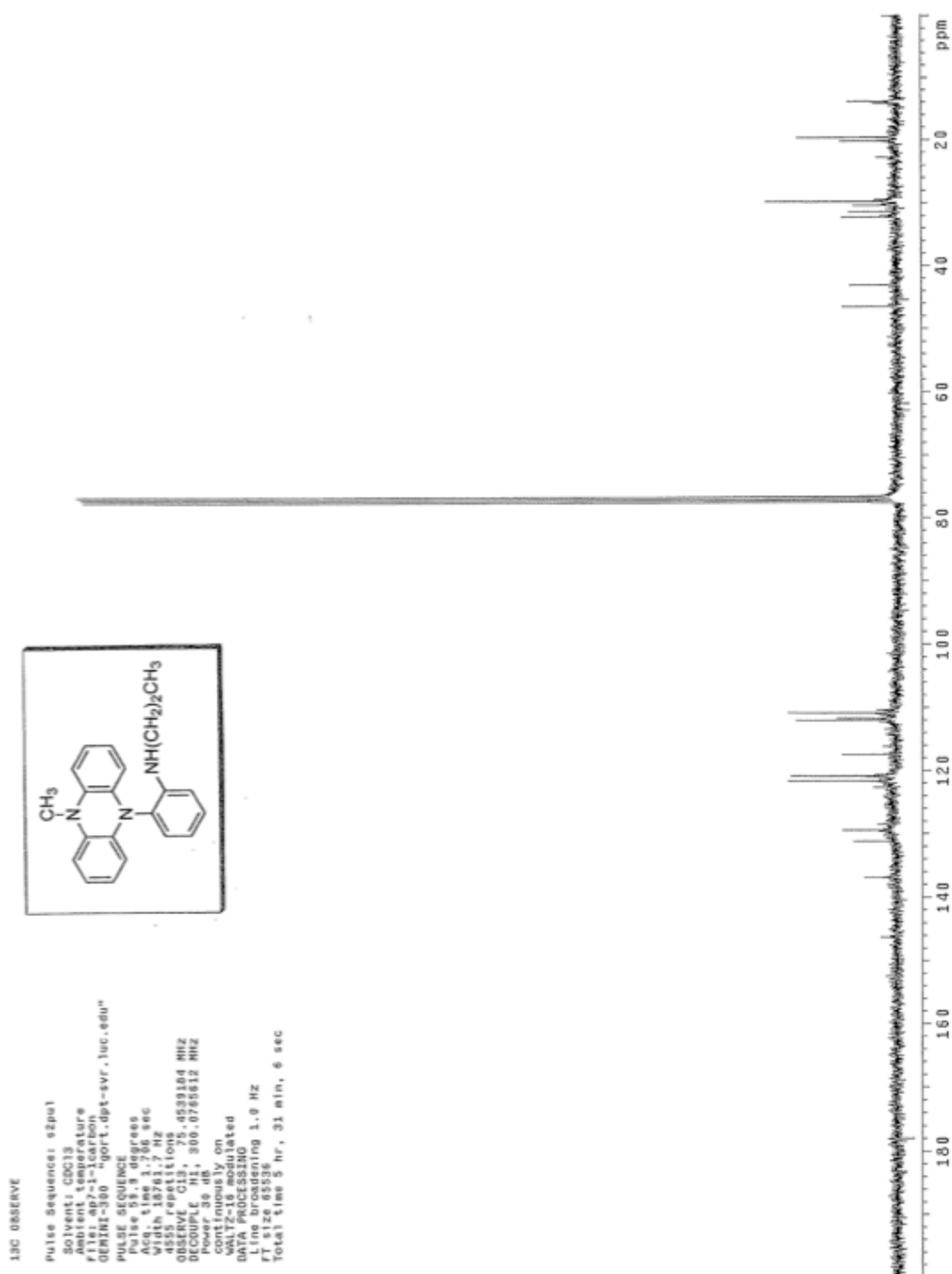
Sample Name	AP6-37-1A	Position	P1-83	Instrument Name	Instrument 1	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	
Data Filename	AP6-37-1A.d	ACQ Method	ESI_ASI_Pos_03122009	Comment		Acquired Time	Success 6/25/2010 11:43:47 AM



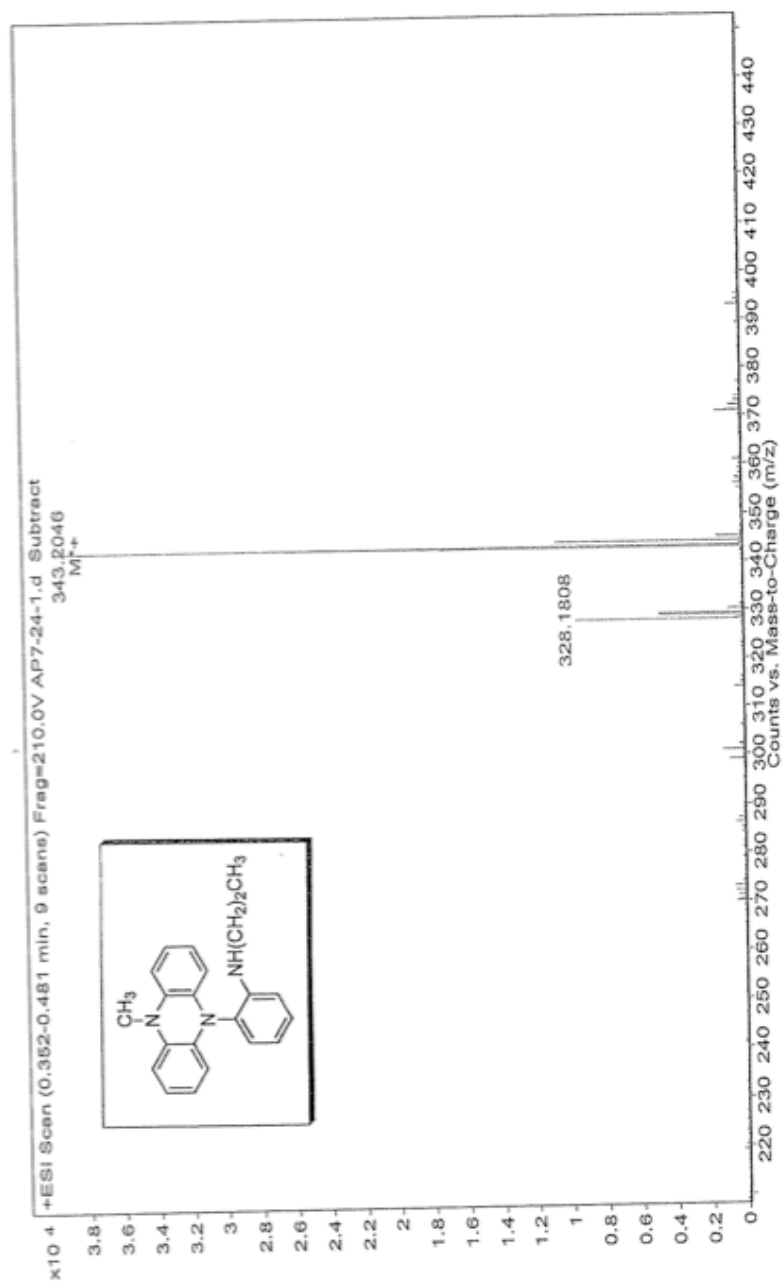
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Acquired Date: 11/11/00
File: m7-24-1crude
GEMINI-300 "gort.dpt-svr.luc.edu"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 1.500 sec
Width 8500.5 Hz
32 repetitions
OBSERVE M1,300.0750634 MHz
DATA PROCESSING
File: s2-12785
Total time 1 min, 33 sec





Sample Name AP7-24-1
Inj Vol 2
Data Filename AP7-24-1.d
Position P1-84
InjPosition
ACQ Method
Instrument Name Sample
SampleType
Comment
User Name
IRM Calibration Status
Acquired Time
Success
6/25/2010 11:46:32 AM



Sample Name AP7-24-1
Inj Vol 2
Data Filename AP7-24-1.d

Position
InjPosition
ACQ Method

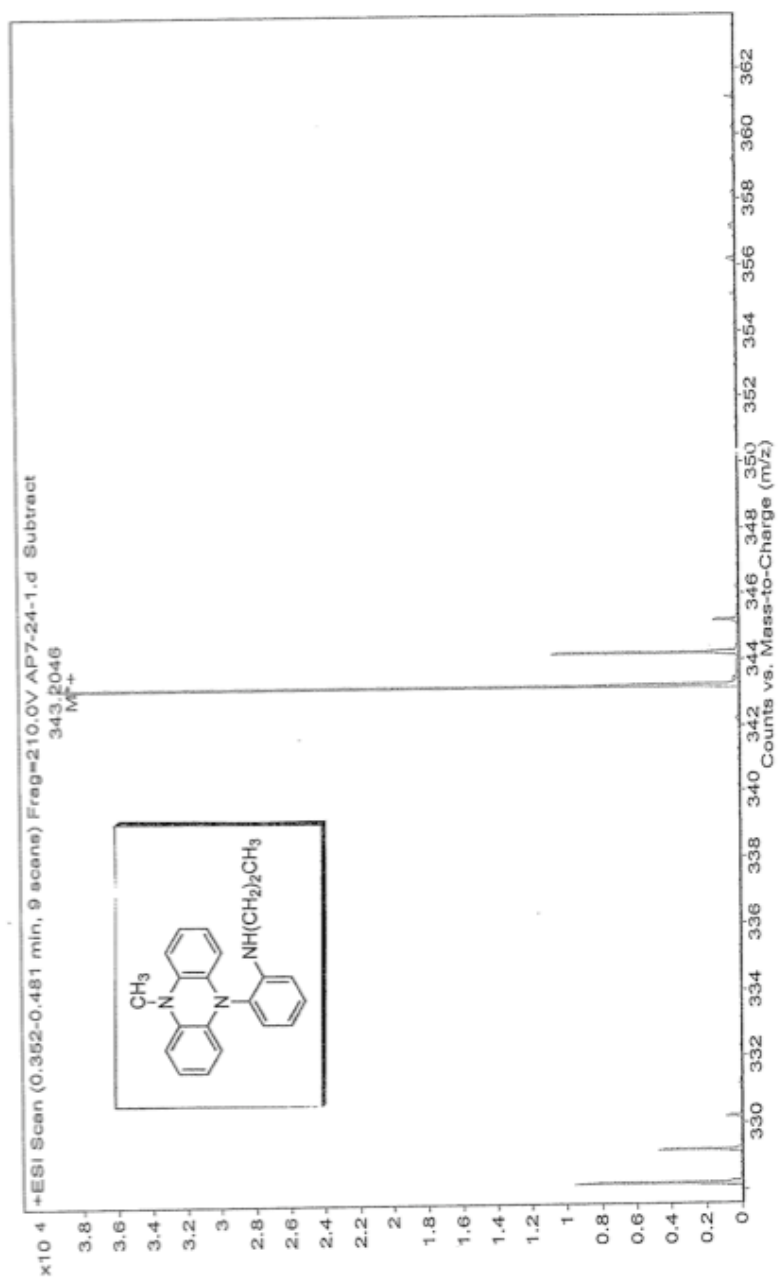
P1-B4
ESL_ASL_Pos_03122009

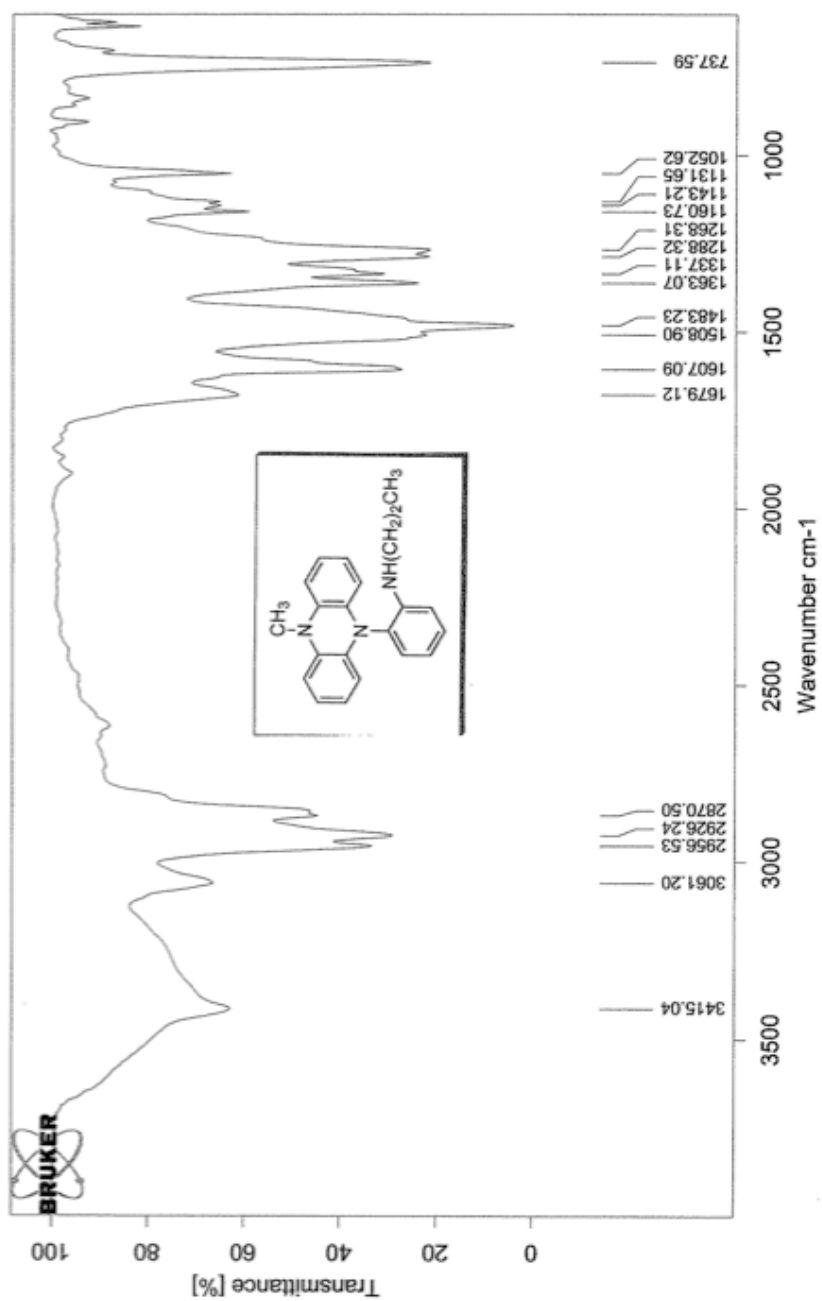
Instrument Name
SampleType
Comment

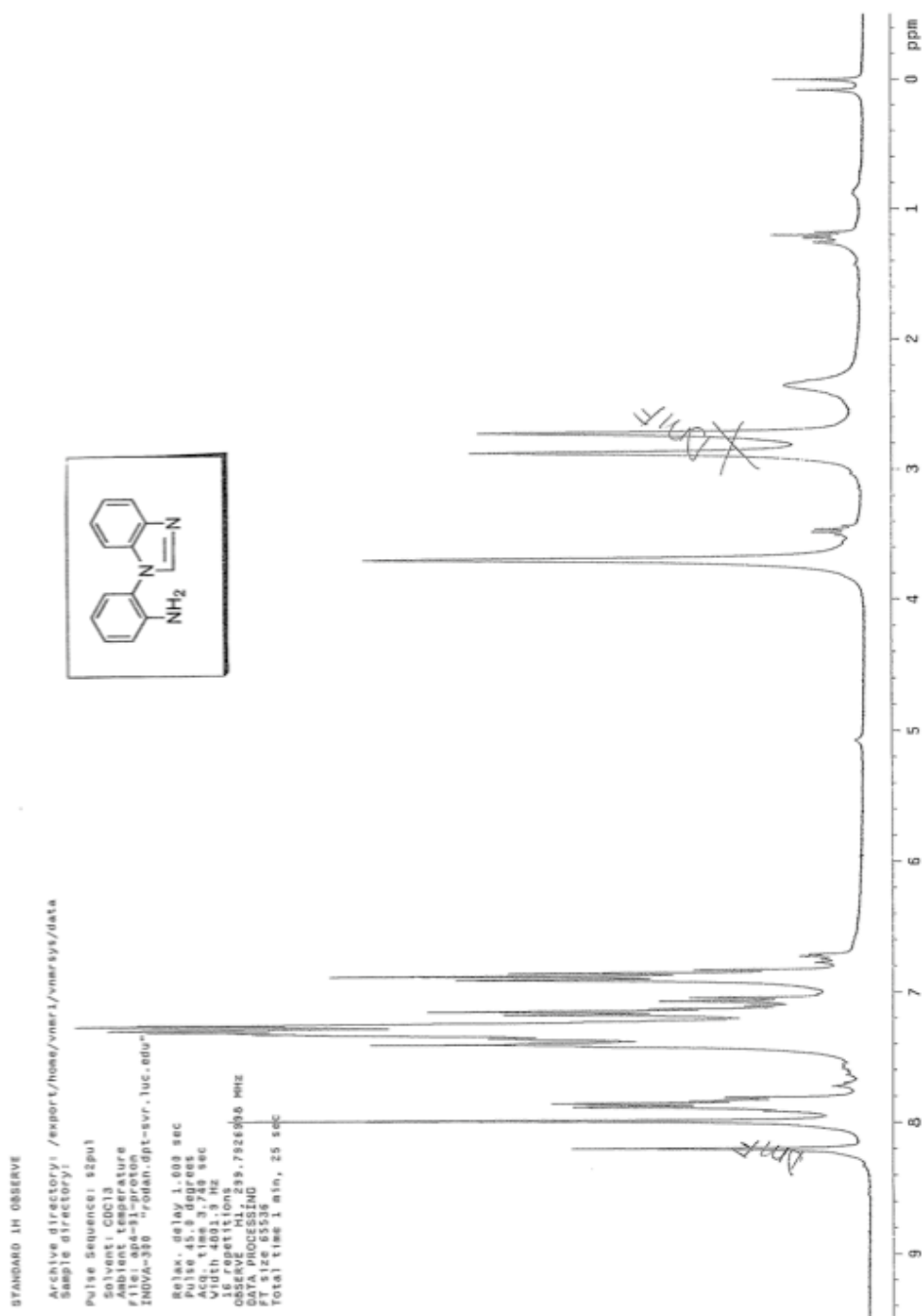
Instrument 1
Sample

User Name
IRM Calibration Status
Acquired Time

Success
6/25/2010 11:46:32 AM







REFERENCES

1. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons Ltd.: West Sussex, England, 2000; , pp 745.
2. Cragg, P. J. *A Practical Guide to Supramolecular Chemistry*; John Wiley & Sons Ltd.: West Sussex, England, 2005; , pp 203.
3. Beer, P.; Gale, P.; Smith, D. *Supramolecular Chemistry*; Oxford University Press Inc.: New York, 1999; , pp 92.
4. Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991; , pp 313.
5. Vögtle, F. *Cyclophane Chemistry: Synthesis, Structures and Reactions*; John Wiley & Sons Ltd: West Sussex, England, 1993; , pp 501.
6. Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *12*, 3908-3909.
7. Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *2*, 293-299.
8. Cameron, K. S.; Fielding, L.; Mason, R.; Muir, A. W.; Rees, D. C.; Thorn, S.; Zhang, M. *Bioorg. Med. Chem. Lett.* **2002**, *5*, 753-755.
9. Ettmayer, P.; Billich, A.; Hecht, P.; Rosenwirth, B.; Gstach, H. *J. Med. Chem.* **1996**, *17*, 3291-3299.
10. Richard, J.; Pamart, M.; Hucher, N.; Jabin, I. *Tetrahedron Lett.* **2008**, *24*, 3848-3852.
11. Conejo-Garcia, A.; Campos, J. M.; Sanchez-Martin, R. M.; Gallo, M. A.; Espinosa, A. *J. Med. Chem.* **2003**, *17*, 3754-3757.
12. Bruno, G.; Cafeo, G.; Kohnke, F. H.; Nicolo, F. *Tetrahedron* **2007**, *40*, 10003-10010.
13. Kohnke, F. H.; Cafeo, G.; La Torre, G. L.; Parisi, M. F.; Nascone, R. P.; White, A. J.; Williams, D. J. *Chemistry : a European journal* **2002**, *14*, 3148.
14. Cronin, L. L. e. *Angewandte Chemie. International edition in English* **2006**, *22*, 3576-3578.

15. Puchta, R.; van Eldik, R. *Eur. J. Inorg. Chem* **2007**, 8, 1120-1127.
16. Chen, J.; Galanakis, D.; Ganellin, C. R.; Dunn, P. M.; Jenkinson, D. H. *J. Med. Chem.* **2000**, 19, 3478-3481.
17. Campos, R. J.; Galanakis, D.; Piergentili, A.; Bhandari, K.; Ganellin, C. R.; Dunn, P. M.; Jenkinson, D. H. *J. Med. Chem.* **2000**, 3, 420-431.
18. Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew Chem Int Ed Engl* **2007**, 14, 2366-2393.
19. Collet, A. *Tetrahedron* **1987**, 24, 5725-5759.
20. Collet, A. *Comprehensive Supramolecular Chemistry* **1996**, 281-303.
21. Steed, J. W.; Zhang, H.; Atwood, J. L. *Supramolecular Chemistry* **1996**, 1, 37-45.
22. Burlinson, N. E.; Ripmeester, J. A. *Journal of Inclusion Phenomena* **1984**, 4, 403-409.
23. Nierengarten, J. *Fullerenes, Nanotubes & Carbon Nanostructures* **2005**, 229-242.
24. Harig, M.; Neumann, B.; Stammeler, H.; Kuck, D. *European Journal of Organic Chemistry* **2004**, 11, 2381-2397.
25. Hardie, M. J.; Ahmad, R.; Sumby, C. J. *New Journal of Chemistry* **2005**, 10, 1231-1240.
26. Ahmad, R.; Franken, A.; Kennedy, J. D.; Hardie, M. J. *Chemistry : A European Journal* **2004**, 9, 2190-2198.
27. Ahmad, R.; Hardie, M. J. *Supramolecular Chemistry* **2006**, 1, 29-38.
28. Zimmermann, H.; Tolstoy, P.; Limbach, H.; Poupko, R.; Luz, Z. *J Phys Chem B* **2004**, 48, 18772-18778.
29. Lutz, M. R.; French, D. C.; Rehage, P.; Becker, D. P. *Tetrahedron Lett.* **2007**, 36, 6368-6371.
30. David C. French; Marlon R. Lutz, J.; Chichi Lu; Matthias Zeller; and Daniel P. Becker *J. Phys. Chem. A* **2009**, 8258.
31. Lutz, M. R., Jr.; Zeller, M.; Becker, D. P. *Tetrahedron Lett.* **2008**, 34, 5003-5005.

32. Collet, A.; Dutasta, J. P.; Lozach, B.; Canceill, J. *Top. Curr. Chem.* **1993**, *Supramolecular Chemistry I*, 103-129.
33. Matsubara, H.; Hasegawa, A.; Shiwaku, K.; Asano, K.; Uno, M.; Takahashi, S.; Yamamoto, K. *Chem. Lett.* **1998**, *9*, 923-924.
34. Matsubara, H.; Shimura, T.; Hasegawa, A.; Semba, M.; Asano, K.; Yamamoto, K. *Chem. Lett.* **1998**, *11*, 1099-1100.
35. Matsubara, H.; Oguri, S.; Asano, K.; Yamamoto, K. *Chem. Lett.* **1999**, *5*, 431-432.
36. Brotin, T.; Dutasta, J. *Chem. Rev. (Washington, DC, U. S.)* **2009**, *1*, 88-130.
37. Canceill, J.; Collet, A.; Gottarelli, G.; Palmieri, P. *J. Am. Chem. Soc.* **1987**, *21*, 6454-6464.
38. Huber, G.; Brotin, T.; Dubois, L.; Desvaux, H.; Dutasta, J.; Berthault, P. *J. Am. Chem. Soc.* **2006**, *18*, 6239-6246.
39. Huber, J. G.; Desaux, H.; Dutasta, J.; Brotin, T.; Berthault, P. *J. Phys. Chem. A* **2004**, 9608.
40. Rio, Y.; Nierengarten, J. *Tet. Let.* **2002**, 4321.
41. Von Deuten, K.; Klar, G. *Zeitschrift fuer Naturforschung, Teil B: Anorganische Chemie, Organische Chemie* **1981**, *12*, 1526-1531.
42. Weiss, T.; Schulz, P.; Klar, G. *Zeitschrift fuer Naturforschung, Teil B: Anorganische Chemie, Organische Chemie, Biochemie, Biophysik, Biologie* **1974**, *3-4*, 156-158.
43. Woodard, C. M.; Hughes, G.; Massey, A. G. *Journal of Organometallic Chemistry* **1976**, *1*, 9-19.
44. Weiss, T.; Klar, G. *Zeitschrift fuer Naturforschung, Teil B: Anorganische Chemie, Organische Chemie* **1979**, *3*, 448-450.
45. Von Deuten, K.; Kopf, J.; Klar, G. *Crystal Structure Communications* **1979**, *3*, 569-575.
46. Von Deuten, K.; Kopf, J.; Klar, G. *Crystal Structure Communications* **1979**, *3*, 721-728.
47. Kopf, J.; Von Deuten, K.; Klar, G. *Crystal Structure Communications* **1979**, *4*, 1011-1016.

48. Von Deuten, K.; Klar, G. *Crystal Structure Communications* **1981**, *2*, 757-764.
49. Hara, H.; Watanabe, S.; Yamada, M.; Hoshino, O. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1996**, *7*, 741-745.
50. Iranzo, O.; Elmer, T.; Richard, J. P.; Morrow, J. R. *Inorg. Chem.* **2003**, *24*, 7737-7746.
51. Dussalt, D.; Friedle, S.; Zompa, L. J. *Inorg. Chim. Acta* **2004**, *5*, 1478-1486.
52. Benniston, A. C.; Ellis, D.; Farrugia, L. J.; Kennedy, R.; Peacock, R. D.; Walker, S. *Polyhedron* **2002**, *3*, 333-342.
53. Weisman, G. R.; Vachon, D. J.; Johnson, V. B.; Gronbeck, D. A. *Journal of the Chemical Society, Chemical Communications* **1987**, *12*, 886-887.
54. Warden, A.; Graham, B.; Hearn, M. T. W.; Spiccia, L. *Org. Lett.* **2001**, *18*, 2855-2858.
55. Chong, H.; Garmestani, K.; Bryant, L. H., Jr.; Milenic, D. E.; Overstreet, T.; Birch, N.; Le, T.; Brady, E. D.; Brechbiel, M. W. *J. Med. Chem.* **2006**, *6*, 2055-2062.
56. Levy, S. G.; Jacques, V.; Zhou, K. L.; Kalogeropoulos, S.; Schumacher, K.; Amedio, J. C.; Scherer, J. E.; Witowski, S. R.; Lombardy, R.; Koppetsch, K. *Org. Process Res. Dev.* **2009**, *3*, 535-542.
57. Chong, H.; Ma, X.; Le, T.; Kwamena, B.; Milenic, D. E.; Brady, E. D.; Song, H. A.; Brechbiel, M. W. *J. Med. Chem.* **2008**, 118.
58. Cruz-Campa, I.; Arzola, A.; Santiago, L.; Parsons, J. G.; Varela-Ramirez, A.; Aguilera, R. J.; Noveron, J. C. *Chem. Commun. (Cambridge, U. K.)* **2007**, *28*, 2944-2946.
59. Sheng, X.; Lu, X.; Zhang, J.; Chen, Y.; Lu, G.; Shao, Y.; Liu, F.; Xu, Q. *J. Org. Chem.* **2007**, *5*, 1799-1802.
60. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *Cross-Coupling Reactions*, 131-209.
61. Wolfe, J. P.; Wagaw, S.; Marcoux, J.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *12*, 805-818.
62. Yang, B. H.; Buchwald, S. L. *Journal of Organometallic Chemistry* **1999**, *1-2*, 125-146.

63. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. *M. J. Org. Chem.* **1999**, *15*, 5575-5580.
64. Hartwig, J. F. *Angewandte Chemie, International Edition* **1998**, *15*, 2090-2093.
65. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *12*, 852-860.
66. Hartwig, J. F. *Pure and Applied Chemistry* **1999**, *8*, 1417-1423.
67. Negishi, E.; de Meijere, A.; Backvall, J. E.; Cacchi, S.; Hayashi, T.; Ito, Y.; Kosugi, M.; Murahashi, S.; Oshima, K.; Yamamoto, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*. John Wiley & Sons, Inc.: New York, 2002; Vol. 1, pp 1659.
68. Ley, S. V.; Thomas, A. W. *Angewandte Chemie, International Edition* **2003**, *44*, 5400-5449.
69. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *13*, 5164-5173.
70. Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *22*, 8236-8241.
71. Bidman, T. A. *Russian Journal of General Chemistry (Translation of Zhurnal Obshchei Khimii)* **2004**, *9*, 1433-1434.
72. Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angewandte Chemie, International Edition* **2005**, *9*, 1371-1375, S1371/1-S1371/79.
73. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *48*, 12706.
74. Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2008**, *8*, 3047-3062.
75. Brunel, J. M. *Mini-Rev. Org. Chem.* **2004**, *3*, 249-277.
76. Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *14*, 2413-2415.
77. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *30*, 5327-5330.
78. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angewandte Chemie, International Edition in English* **1995**, *12*, 1348-1350.
79. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *4*, 1144-1157.
80. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *30*, 7215-7216.

81. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *26*, 9135-9142.
82. Sturmer, R. *Angew. Chem., Int. Ed.* **1999**, *22*, 3307-3308.
83. Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *12*, 4101-4111.
84. Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. --Eur. J.* **2006**, *19*, 5142-5148.
85. Zhang, S.; Echegoyen, L. *Comptes Rendus Chimie* **2006**, *7-8*, 1031-1037.
86. Tietze, M.; Iglesias, A.; Merisor, E.; Conrad, J.; Klaiber, I.; Beifuss, U. *Org. Lett.* **2005**, *8*, 1549-1552.
87. Black, D. S.; Rothnie, N. E. *Aust. J. Chem.* **1983**, *6*, 1141-1147.
88. Koutentis, P. A. *ARKIVOC (Gainesville, FL, U. S.)* **2002**, *6*, 175-191.
89. Wilshire, J. F. K. *Aust. J. Chem.* **1988**, *6*, 995-1001.
90. Herres-Pawlis, S.; Neuba, A.; Seewald, O.; Seshadri, T.; Egold, H.; Floerke, U.; Henkel, G. *Eur. J. Org. Chem.* **2005**, *22*, 4879-4890.
91. Atkins, T. J. *J. Am. Chem. Soc.* **1980**, *20*, 6364-6365.
92. Wilshire, J. F. K. *Australian Journal of Chemistry* **1988**, *6*, 995-1001.
93. Sanz, R.; Fernandez, Y.; Castroviejo, M. P.; Perez, A.; Fananas, F. J. *J. Org. Chem.* **2006**, *16*, 6291-6294.
94. Loones, K. T. J.; Maes, B. U. W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* **2005**, *43*, 10338-10348.
95. Nilsson, P.; Olofsson, K.; Larhed, M. *Top. Curr. Chem.* **2006**, *Microwave Methods in Organic Synthesis*, 103-144.
96. Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *17*, 6814-6816.
97. Jensen, T. A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* **2004**, *15*, 4936-4947.
98. Sanz, R. *Org. Prep. Proced. Int.* **2008**, *3*, 215-291.

99. Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan Wheaton, C. *J. Am. Chem. Soc.* **1953**, 3290-3291.
100. Roberts, J. D.; Vaughan, C. W., Jr.; Carlsmith, L. A.; Semenow, D. *J. Am. Chem. Soc.* **1956**, 611-614.
101. Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, 6, 2045-2050.
102. Kampmeier, J. A.; Hoffmeister, E. *J. Am. Chem. Soc.* **1962**, 3787-3788.
103. Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, 1549.
104. Kessar, S. V. *Acc. Chem. Res.* **1978**, 7, 283-288.
105. Biehl, E. R.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, 8, 275-281.
106. Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, 1691-1697.
107. Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, 91-108.
108. Biehl, E. R. Advances in Nitrogen Heterocycles. In JAI Press, Inc: 2000; Vol. 4, pp 251.
109. Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, 8, 3198-3209.
110. Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, 1, 99-102.
111. Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, 24, 4673-4675.
112. Rao, U. *ARKIVOC (Gainesville, FL, United States)* **2004**, 1, 88.
113. Wade, L. G. *Organic Chemistry*; Pearson Education, Inc.: Upper Saddle River, NJ, 2006; , pp 1262.
114. Yoshida, H.; Sugiura, S.; Kunai, A. *Org. Lett.* **2002**, 16, 2767-2769.
115. Cairns, J.; Clarkson, T. R.; Hamersma, J. A. M.; Rae, D. R. *Tetrahedron Lett.* **2002**, 8, 1583-1585.
116. La Regina, G.; Silvestri, R.; Gatti, V.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. *Bioorg. Med. Chem.* **2008**, 22, 9729-9740.

117. Musachio, J. L.; Hong, J.; Ichise, M.; Seneca, N.; Brown, A. K.; Liow, J.; Halldin, C.; Innis, R. B.; Pike, V. W.; He, R.; Zhou, J.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2006**, *12*, 3101-3104.
118. Cutri, S.; Diez, A.; Bonin, M.; Micouin, L.; Husson, H. *Org. Lett.* **2005**, *10*, 1911-1913.
119. Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn.* **1988**, *6*, 2226-2228.
120. Klaerner, F.; Kahlert, B. *Acc. Chem. Res.* **2003**, *12*, 919-932.
121. Mas, T.; Pardo, C.; Elguero, J. *Helv. Chim. Acta* **2005**, *6*, 1199-1207.
122. Harmata, M. *Acc. Chem. Res.* **2004**, *11*, 862-873.
123. ITOH, T. T. a. *Tetrahedron* **2004**, *31*, 6649-6655.
124. ap1-67-1 and ap1-71-1 were made according to the procedure listed at http://basti.borec.cz/_english/e_cui.html

VITA

Andria M. Panagopoulous, a native Chicagoan, began her career with dreams of becoming a surgeon. In pursuit of this dream, she enrolled as an undergraduate student at Chicago's Jesuit University, Loyola. It was at Loyola where she was given the opportunity to do research in a biochemistry lab, which enabled her to recognize her true passion: research. This discovery did not mar her medical interest; rather it opened her eyes to new opportunities within the medical profession, not as surgeon, but as scientist. Motivated with her newfound passion and zeal for research, she hopes to continue her research and maximize her knowledge of synthetic organic chemistry. Specifically, she desires to focus on synthetic organic chemistry in relation to medicinal chemistry, with a wish that one day her work will have a positive impact on humanity.

Outside of the lab, Andria spreads her passion for chemistry and education as a role model and volunteer for an inner-city youth group for the young women of tomorrow. Additionally, she cultivates her personal interest through reading, maintains mental stability through yoga and ballroom dancing, and reposes with a pleasant wine and superb cuisine.